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Original Articles

by

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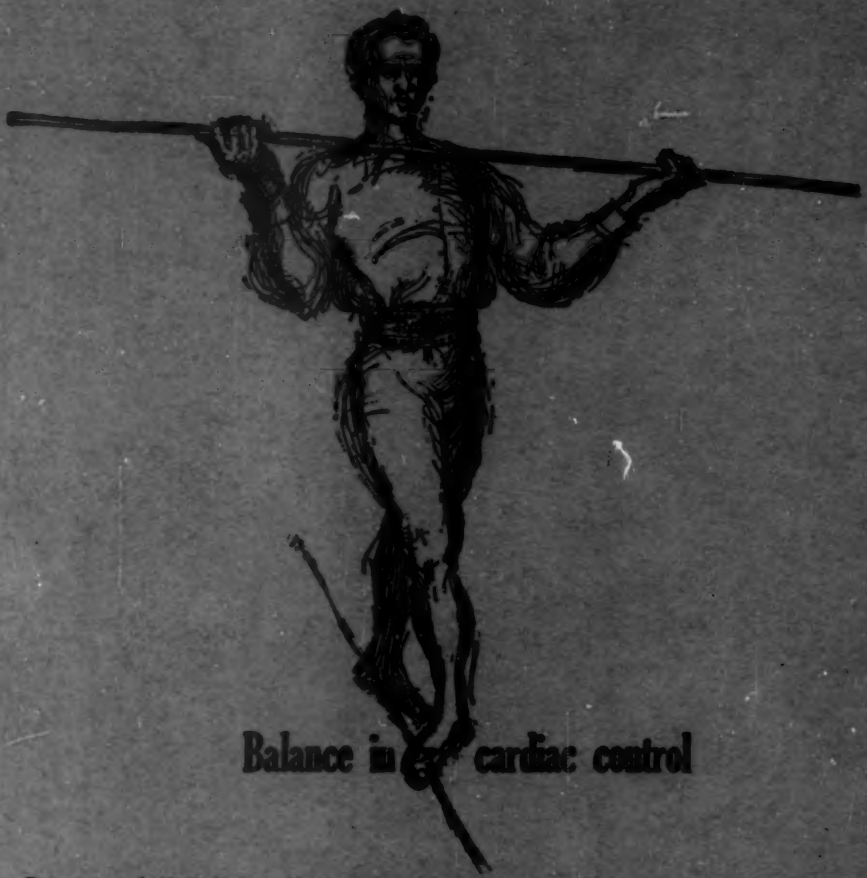

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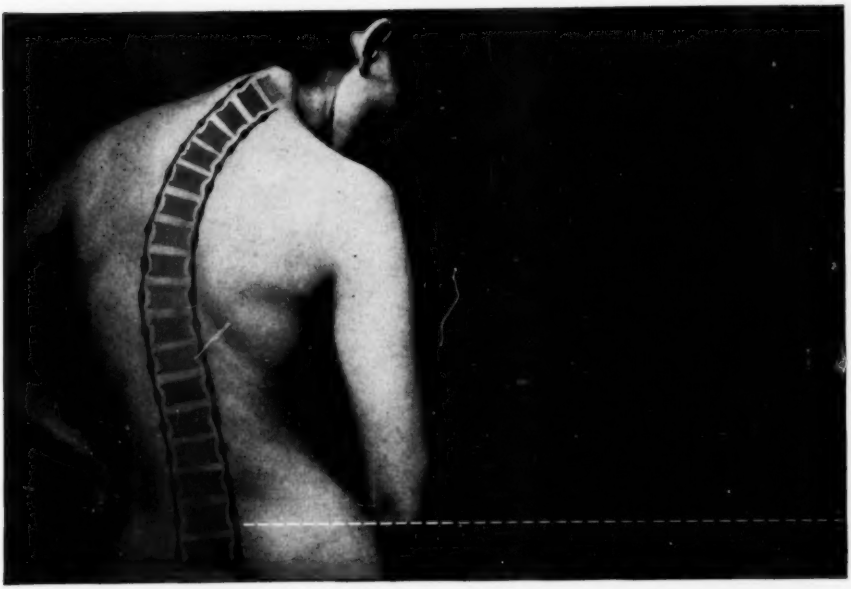

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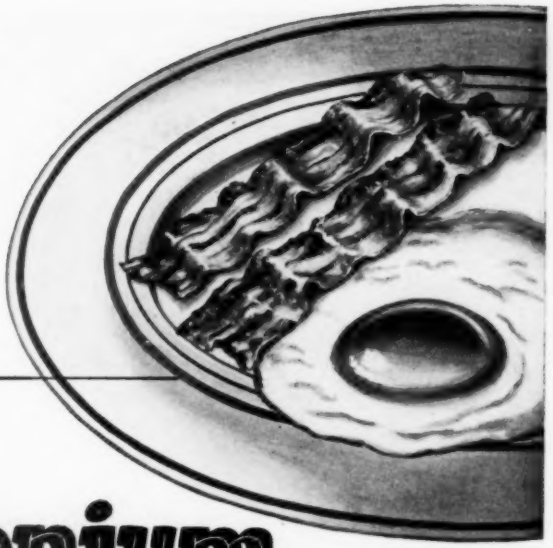

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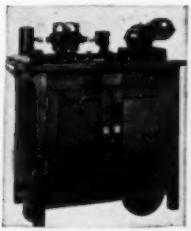

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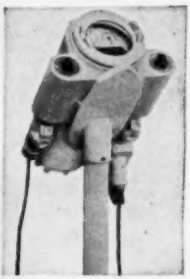

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BULLETIN OF
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OF MEDICINE

VOL. 28, NO. 12 DECEMBER 1952

RECENT ADVANCES IN THE MEDICAL MANAGEMENT OF PEPTIC ULCER*

CHARLES A. FLOOD

Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University, New York City

A CONSIDERABLE number of new remedies have been proposed in recent years for the medical treatment of peptic ulcer.[1] The evaluation of these new methods of treatment is a difficult undertaking, usually requiring a considerable period of clinical observation. Inasmuch as the basic local mechanisms which are responsible for peptic ulceration are still incompletely understood, the final appraisal of new forms of treatment depends almost entirely on clinical trial, even though a proposed remedy has an acceptable rationale.

METHODS OF ASSAY OF REMEDIES FOR ULCER

One is concerned in the evaluation of new remedies with their effect upon gastric secretion and motility and with their ability to prevent or heal ulcers in experimental animals. Unfortunately, the effects of various therapeutic procedures as observed on the experimental animal do not always correlate well with the result obtained in clinical usage. Clinical

* Presented in the Friday Afternoon Lecture Series, March 28, 1952, at The New York Academy of Medicine.

results in ulcer therapy may be measured in several ways. These include the rate of symptomatic relief reported by patients, the rapidity of healing of ulcer craters, as observed in serial radiologic examinations, or finally, the long-term effects in preventing recurrences over a period of years.

The natural history of peptic ulcer is characterized by periods of apparently spontaneous exacerbation and remission and is such that rather prompt symptomatic improvement can be anticipated with almost any method of therapy in the majority of patients. Pain may be relieved quickly by the use of placebos. Daily injections of saline or distilled water, administered with strong assurance of their merit, have been followed by symptomatic relief in one-half to two-thirds of the patients so treated.[2] It is likewise well known that any change in therapy, such as the administration of a new remedy or hospitalization alone, will often be followed by a prompt subsidence of pain due to ulcer.

The relief of symptoms with placebos emphasizes the importance of psychologic factors in the disease. The relationship of emotional tension to symptoms was also illustrated convincingly by experiences in the armed services with patients with ulcer during World War II.[3, 4] A number of studies indicated that there was a close correlation between the morale factor and the rate of response to treatment in soldiers with peptic ulcer. Treatment of a type which in civilian life would be expected to yield symptomatic relief and healing of the lesion, was unsuccessful in a large proportion of soldiers.

Objective evaluation of the effect of treatment in terms of the rate of healing of the lesion may be carried out by means of serial x-ray examinations. Available data indicate that the average healing time of gastric ulcer is approximately seven weeks. In a series of fifty-one patients with gastric ulcer studied at the Presbyterian Hospital, the average healing time on conventional conservative therapy was about forty days.[5] In a number of patients the crater could no longer be demonstrated on reexamination after two or three weeks of treatment. In a few patients who declined surgery, the ulcer crater was still demonstrable after more than twelve weeks of therapy.

A recent report that 80 per cent of gastric ulcers heal at the usual rate with placebos alone, casts doubt upon the value of study of the rate of healing as a method of evaluating treatment. This observation also emphasizes the tendency to apparently spontaneous remissions in peptic

ulcer and again raises the question of the importance of psychologic factors. The rate of healing of ulcer craters in the stomach is also not a practical method of evaluating new forms of treatment because the ever-present fear that an ulcer crater may be a manifestation of early malignancy, renders such patients unsuitable for this type of study.

The rate of healing of ulcer craters in the duodenum appears to be approximately the same as that found in gastric ulcer under conventional medical treatment. In duodenal ulcer, the technical difficulty of determining the presence or absence of a crater in a deformed duodenal bulb with reasonable certainty, diminishes the value of this method of approach to the problem.

Whereas conventional medical therapy is effective in relieving the acute attack in approximately 90 per cent of patients with ulcer, the long-term results of medical management are far from satisfactory. Newly proposed remedies must be assayed in terms of their prophylactic effect over a period of years. Follow-up study of patients with duodenal ulcer following an initial period of hospital therapy of the standard variety consisting of diet, alkalies and sedation, indicates that recurrence of symptoms takes place at an average rate of once every two years.[6] In gastric ulcer, the recurrence rate is essentially the same. Wide variations occur, however, and in the average patient with ulcer, the pattern of behavior of the disease appears to be almost completely unpredictable. It is evident that in order to evaluate a new remedy in terms of remote results, a period of at least one or two years is required. The selection of cases for study influences the results to be anticipated. In a series of patients with mild symptoms of duodenal ulcer, which had almost never been incapacitating, the recurrence rate on the standard type of medical management, was once every four years. On the other hand, a series of patients with relatively intractable pain from ulcer during hospital treatment, had a subsequent recurrence rate of approximately once a year.

Choice of Antacids

It seems clear that the concentration of hydrochloric acid in the stomach bears an important relation to the mechanism of pain in peptic ulcer. The instillation of approximately 0.1 hydrochloric acid into the stomach of the patient with ulcer during the active phase of the disease, will reproduce pain. There is also a large body of evidence which indi-

cates that hydrochloric acid acts to delay healing. Routine medical management depends on the use of frequent feedings and alkalies, partially to neutralize acid. For this purpose, a large number of antacids are available and the selection of a particular substance and the dosage to be administered depends chiefly upon the degree of neutralization which it is desired to maintain. The possibility of undesirable side effects must also be considered.

The recent studies of Kirsner and others,[7] using serial aspirations of gastric contents for titration have shown that a mixture of calcium carbonate and a magnesium salt is the most effective combination of the commonly used alkalies if complete, or nearly complete, neutralization is desired. With mixtures of these salts, constipation or diarrhea can usually be avoided. Aluminum hydroxide, which at present enjoys wide-spread use, must be administered in large doses in order to approach neutralization of acid and usually requires the addition of magnesium salts to counteract a constipating effect. Aluminum phosphate may be used to advantage in occasional patients where there is a fear of an excessive loss of phosphates in the stools. Magnesium trisilicate acts somewhat more slowly in neutralizing acid. Clinically, it seems somewhat less effective in relieving pain than mixtures of calcium carbonate and magnesium oxide.

The dosage of alkalies which is commonly used in the treatment of ulcer falls far short of that which is required to approach neutralization of hydrochloric acid. Kirsner and Palmer[7] found, for example, that hourly doses of 2 to 4 grams of calcium carbonate, together with milk and cream and atropine, usually maintain the pH of the gastric contents of the stomach at approximately 4.0 to 5.5. It is common experience that much smaller quantities of alkali are sufficient to relieve pain and there appears to be no convincing evidence that large amounts of alkalies are of more benefit.

There has been surprisingly little work done on the effect of alkalies on ulcer in the experimental animal. Ivy and his coworkers,[8] found that aluminum phosphate apparently reduced the incidence of ulcer in a series of Mann-Williamson dogs and also seemed to aid healing when ulceration was established. Careful studies of the rate of healing of ulcer craters in the human with and without alkali administration, appear to be lacking.

Untoward Effects of Soluble Alkalies: Alkalosis is now encoun-

tered only infrequently in patients with peptic ulcer, probably because patients with organic pyloric obstruction and vomiting are not often treated conservatively for long periods, and also because bicarbonate of soda is employed as an antacid less frequently than formerly. Occasional patients with ulcer are observed who have developed an unusual syndrome characterized by an elevated serum calcium, nitrogen retention and mild alkalosis.[9] Such individuals usually give a history of the ingestion of very large quantities of milk and bicarbonate of soda over a long period of time. Renal dysfunction is manifested by albuminuria, elevation of non-protein nitrogen and abnormal kidney function tests. Radiologic examination may reveal calcification in the renal areas. Improvement occurs when the milk intake is diminished and bicarbonate of soda is discontinued.

Other Antacids: Several new antacids have recently been introduced as substitutes for the inorganic alkalies.[10] These substances combine with hydrogen ion in the stomach and subsequently release it upon reaching an alkaline medium in the small intestine, thus avoiding the possibility of a disturbance in acid base balance. Sodium carboxymethyl cellulose, the salt of a strong base and a weak acid, exchanges sodium for hydrogen ion in the stomach, producing a moderate reduction in acidity.[11] Clinical studies indicate that this substance is effective in relieving pain. It also possesses the advantage of acting as a hydrophyllic colloid and tends to relieve constipation. It has also been reported to have some prophylactic effect in preventing recurrence of ulcer.

Anion exchange resins are also useful as antacids.[12-15] These insoluble bases of large molecular weight, adsorb acid in the stomach and release it later in the intestine. The pain of ulcer is usually relieved rapidly. In one study, the addition of a resin to a modified Sippy regime resulted in an average rate of healing of nineteen days, as compared with thirty-three days in a control group.

Detergents

The use of substances which may inhibit peptic activity as a method of treatment in peptic ulcer has been disappointing. Certain of the alkyl sulfates, namely sodium alkyl sulphate and dodecyl sulphate, inhibit peptic activity without affecting gastric acidity.[16-18] These substances have been reported to have protective anti-ulcer activity in the experimental animal. In the human, these preparations seem to have little effect

on peptic activity in vivo, apparently because the presence of fats interferes with their action. The reported results of therapeutic trial have been variable and at times unsatisfactory in a limited number of patients.

Anticholinergic Drugs

Since the advent of vagotomy, there has been increased interest in the use of cholinergic blocking agents in the treatment of ulcer. Atropine, which apparently acts peripherally at postganglionic nerve endings, inhibits gastric motility but is variable and unpredictable in its effect upon gastric secretion in man. Synthetic analoges of atropine, such as trasentin, syntropan and bentyl hydrochloride, have little effect upon the volume or level of gastric acidity in the dosages used clinically.

Several other groups of drugs have been proposed for altering motor function in patients with peptic ulcer, but have not proved practical for general clinical use. The quaternary ammonium compounds, such as tetra-ethyl ammonium chloride, act by blocking cholinergic impulses at the autonomic ganglia. These drugs depress gastric secretion when administered parenterally. The side effects and the necessity for parenteral administration, make them of little value in the management of ulcer.

Hexamethonium and pentamethonium salts are likewise ganglion blocking agents. These preparations will reduce gastric secretion and motility when administered intramuscularly and the former is apparently also active orally. Postural hypotension is also produced.

Banthine is currently on trial as an anticholinergic drug in the treatment of peptic ulcer.[19-21] It acts chiefly at postganglionic nerve endings. This drug is an effective inhibitor of propulsive motility in clinical dosage, but its effect on gastric secretion is slight or inconsistent. The administration of banthine usually results in prompt relief of pain. Healing of ulcer craters in an average time of 14.4 days has been reported when the drug was added to a modified Sippy regime. It was hoped that prolonged administration of banthine to patients with ulcer after the subsidence of the acute attack, would prevent recurrence. Results to date, however, indicate that recurrences continue to take place with approximately the naturally expected frequency. Of a series of thirty-seven patients who have taken banthine continuously for an average period of nine and a half months, usually in the amount of 50 mg. four

times a day, fifteen patients have suffered from recurrences. Many patients decline to continue to take banthine after recovery from an acute attack, because of unpleasant side effects such as dryness of the mouth and dysuria.

Hormones and Tissue Extracts

Inasmuch as it has been evident that medical treatment based on the principle of neutralization therapy, is inadequate in preventing recurrences in ulcer, efforts have been made to discover a method of treatment which would increase the resistance of the stomach or duodenum to peptic digestion. The amino acid histidine, for example, was considered at one time to exert a protective influence against peptic digestion. Recently a number of substances have been under study in this regard.

Enterogastrone, an extract of intestinal mucosa, has been shown to afford partial protection against the development of ulcer in the Mann-Williamson dog in small doses that do not affect gastric secretion. Clinical studies of the value of enterogastrone have not shown any consistent benefit and, in general, the patients who have been treated have continued to suffer from recurrences.[22, 23]

Another anti-ulcer preparation, kutrol, which is reported to protect against the development of experimental ulcers in the Mann-Williamson dog, is an extract of the urine of the pregnant mare.[24] The protective effect of substances of this type has been attributed to stimulation of fibroblastic proliferation and epithelialization of the mucosa. This substance yields rapid symptomatic relief when administered to patients with active ulcer. The long-term results are not, as yet, reported. A number of other biological extracts, including urogastrone and robuden, suggested for the treatment of ulcer or under study, have not as yet been demonstrated to have any real clinical value.

In contrast with the efforts to obtain a biological extract with anti-ulcer activities, recent experience with cortisone and ACTH has demonstrated rather convincingly that these substances have a destructive effect on patients with ulcerative lesions of the upper gastrointestinal tract.[25] An increasing number of patients who have been under treatment with these substances for unrelated disease, have been observed to suffer a recurrence or even an initial development of a peptic ulcer. Experimental studies support the view that such action may be due to

an inhibition of the formation of granulation tissue or to the stimulation of a hypersecretion of gastric juice.

Prevention of Recurrences

At the present time there appears to be no medical treatment which has been conclusively demonstrated to have a prophylactic effect against recurrences. Various substances which have been proposed as exerting a possible anti-ulcer effect have as yet not been shown to be effective in the human. Conventional neutralization therapy, which is usually very efficacious in controlling the acute phase of the disease, does not appear to decrease the possibility of future recurrences. In a series of patients with duodenal ulcer, a comparison was made of the symptomatic course between those patients who followed a rigid regimen at all times with others who interrupted or discontinued their diets. During the first follow-up year, the group who did not follow a regimen continuously and ate unrestrictedly at times, had a better follow-up record than those who adhered to the prescribed regimen.

It would appear that a rigid ulcer regimen is only of benefit during the period of time required for healing. After healing has occurred, which is approximately one to four months, dietary management can probably be modified and the patient may eat any food which does not produce symptoms of gastric intolerance such as gas or bloating.

Complications of Ulcer

The treatment of the complications of ulcer falls largely within the sphere of the surgeon with the exception of gross hemorrhage. Management of gross hemorrhage may now be considered to be a combined medico-surgical problem.[26-29] With changing methods in the management of hemorrhage, the mortality rate has fallen considerably. At the Presbyterian Hospital, for example, the mortality from gross hemorrhage in duodenal ulcer during the years from 1930 to 1937 was 9.6 per cent; in 1948, the mortality rate was 1.3 per cent. This change can be attributed chiefly to the adequate early treatment of shock and to prompt surgical intervention when it is apparent that bleeding is continuing or recurring under conservative management.

The experience of a number of observers in recent years seems convincing that the shock of hemorrhage should be treated by prompt replacement of blood. With such a program, the proportion of patients

who suffer from continued hemorrhage does not appear to be increased. The prompt administration of 1500 cc., for example, of whole blood during the first twenty-four hours of treatment for massive hemorrhage, followed later by such further amounts of blood as are required to restore normal blood volume, prevents the development of the effects of prolonged anoxia which may, after a time, become irreversible. The clinical picture, estimations of the red blood count, hemoglobin, hematocrit and, when available, the blood volume, serve as a basis for determining the amount of blood which is needed. Should surgical intervention become necessary because of continuing hemorrhage, the risk of operation will be far less if shock has been adequately treated.

In patients with upper gastrointestinal hemorrhage of undiagnosed origin, diagnostic studies should be initiated as soon as possible. Early radiologic examination, as proposed by Hampton in 1937,[27] is useful in ruling out the presence of esophageal varices and may reveal the presence of a gastric or duodenal ulcer which might no longer be demonstrable if x-ray examination is delayed for two weeks. In recent years it has frequently been our practice to x-ray patients with bleeding from an unknown source very early unless they are in poor clinical condition and we have not encountered any untoward sequelae. While an early gastrointestinal series may be very helpful, it should also be emphasized that a repeat examination carried out in the routine manner with pressure films, after the hemorrhage has completely stopped, may yield information not obtained in an earlier study.

In selected patients with upper gastrointestinal bleeding other diagnostic studies may be useful.[28] The bromsulfalein test may aid in ruling out esophageal varices. Caution must be exercised in the interpretation of the results of this test, for bleeding varices may occur in patients who exhibit no dye retention. On the other hand, anemia and shock may result in a mild retention of the dye. Gastric aspiration, as a means of demonstrating that the source of bleeding is high in the gastrointestinal tract, may be helpful. Gastroscopic examination in patients with negative x-rays may reveal the presence of an ulcer in the stomach. It should be carried out, when indicated, within three to ten days after the hemorrhage. If the procedure is delayed beyond two to three weeks, acute ulcers and acute gastritis may have healed.

For years, a controversy has existed concerning the advisability of early feeding in patients with bleeding ulcer. It seems reasonable to

consider that the healing process in a bleeding ulcer would be accelerated by frequent feedings and the use of alkalies to the same extent as in ulcers that are not bleeding, provided that the intake of food does not increase the tendency to hemorrhage.

Since Andresen advocated early feeding in ulcer with hemorrhage about 1927, there have been many studies of the effects of such a program. Although statistical studies are open to question because of differences in the selection of cases, it now seems clear that early feeding is not injurious and provided it is tolerated, it should be used to maintain the nutritional and metabolic requirements of the patient as well as for the treatment of the local lesion.

Medical management has little to offer in the treatment of patients with the other common complications of ulcer, persistent obstruction and perforation. Recent reports of conservative management of perforation with intubation and antibiotics, are of interest.[30] While it seems unlikely that this method will replace surgical intervention, it may constitute a valuable alternative if a patient sustains a perforation in a place where a qualified surgeon and proper operative facilities are not available.

Summary

In reviewing the current status of conservative treatment of peptic ulcer, one is led to the conclusion that the preferred method of management continues to be a program consisting chiefly of frequent bland feedings and alkalies. Sedatives and drugs which depress gastrointestinal motility, may be added to the schedule of treatment.

Other suggested methods of treatment usually yield satisfactory immediate results. In view of the tendency of the disease toward spontaneous remission and also because of psychologic factors, the merits of any proposed method of therapy are difficult to appraise.

As yet there is no medical treatment which has been demonstrated conclusively to have a prophylactic effect against recurrences. Various substances which have been suggested as exercising an anti-ulcer action, have not been shown, as yet, to be effective in patients with ulcer. Prolonged adherence to a conventional type of medical regimen has also not been found to decrease the possibility of recurrence. Medical management usually yields very satisfactory immediate results. At present, recurrences can usually be expected after a lapse of time and it remains

for the future to provide a method of medical therapy which will prevent them.

Hemorrhage from ulcer should be treated with prompt measures for the control of shock. Combined management by the surgeon and internist, employing early and adequate transfusions and early selection for surgical intervention of those patients with evidence of continuing hemorrhage, has reduced the mortality from bleeding ulcer considerably.

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RECENT DEVELOPMENTS IN THE SURGERY OF PEPTIC ULCER*

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THE one outstanding development in the surgery of peptic ulcer in the past nine years has been the renewed interest in the use of bilateral vagotomy. Sufficient time has now elapsed to appraise its effectiveness not only alone, but in combination with either gastroenterostomy or subtotal gastrectomy in the therapy of duodenal ulcer, and its value in the treatment of gastrojejunal ulceration. It is the purpose of this communication to consider briefly these problems.

While the surgical mortality has been definitely lowered, the postoperative morbidity minimized, and the follow-up results steadily improved, duodenal ulcer should be considered primarily a medical problem. Cases should not be operated upon unless complications develop against which conservative therapy is of little avail, or its continuation is dangerous. These are acute perforation, persistent pain failing to respond to medical measures, intractable pyloric stenosis, occasionally massive hemorrhage during the acute phase, and cases in which the bleeding has been recurrent. Yet even with these present indications, less than 15 per cent of duodenal ulcers will require operative intervention.

Thorough and careful preoperative preparation is a "sine qua non" if the mortality and postoperative morbidity are to be kept at a minimum. It is basically essential that electrolytic imbalances, dehydration, avitaminosis, hypoproteinemia and anemia be carefully corrected prior to operation. Gastric dilatation with retention and vomiting must be adequately treated by hot gastric lavages and appropriate parenteral fluids, and if in spite of these measures an alkalosis persists, a preliminary jejunostomy for alimentation may become mandatory. While cases of massive hemorrhage are being operated upon at an early period and in

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increasing numbers in many clinics, they are still being conservatively managed on our medical services with the acquiesence of the surgeons. In the past ten years, 1939 to 1948, there were two hundred and twenty-seven proven cases of acutely bleeding duodenal ulcer in which the hemoglobin fell to 60 per cent or lower. None of these patients was treated surgically. There were nine hospital deaths, a mortality of 3.9 per cent. This conservative attitude may be considered too extreme, but it is felt that in the overwhelming majority of cases there is a tendency for hemorrhage to stop spontaneously, and it is extremely difficult to select for operation only those few patients who might otherwise bleed to death. Perhaps patients who are not stabilized by blood transfusions within forty-eight hours after admission should be explored.[1] But by and large, it is extremely doubtful that the resultant surgical mortality would be lower than 4 per cent. However, at present it is our policy to send all cases recovering from an acute hemorrhage to a convalescent home for recuperation for six weeks, and those in whom there has been a history of previous hemorrhages, are urged to return for radical surgery.

The question of the type of operation to be performed for duodenal ulcer has always been controversial. Formerly it was a question of gastroenterostomy or gastric resection, and now, either of these often combined with vagotomy. No one procedure can be categorically applied to all patients. In any given case an operation should be selected which will entail the minimal risk, and will give clinical freedom from symptoms, allow a return to work, and afford the greatest protection against recurrence of ulceration.

These criteria in our experience have been best fulfilled by gastric resection which may be offered with a very low mortality to about 80 per cent of our patients. Almost thirty years have elapsed since this clinic first advocated subtotal gastrectomy of the Billroth 2 type as the procedure of choice for duodenal ulcer instead of gastroenterostomy and the various types of pyloroplasties. At first there was strong opposition to this so-called radical operation, but it was gradually adopted by most surgeons as the increasing incidence of gastrojejunal ulceration following gastroenterostomy became apparent, and the excellent results obtained by subtotal gastrectomy became known.

However, in 1943,[2] the advisability and desirability of gastric resection was again challenged when bilateral vagotomy alone was revived and advocated as a definitive curative procedure in cases of chronic

duodenal ulcer without obstruction. At first this technically simple operation was enthusiastically received because its operative mortality was extremely low. Division of the vagi which interrupts the psychic phase of gastric secretion undoubtedly lowers the total and free acid secretion, especially during the night, produces hypomotility, eliminates pain, and in many cases causes the ulcer to heal. But, unfortunately, a vagotomy either complete or incomplete, was often followed by a loss of gastric tone with dilatation of the stomach, producing nausea, vomiting and foul eructations. Moreover the ulcer did not always heal, occasionally perforated, and frequently recurred. The eventual universal dissatisfaction following bilateral vagotomy as a sole procedure is evidenced by the fact that it has now been practically abandoned. Even its most ardent proponents who still prefer it to subtotal gastrectomy now routinely combine infradiaphragmatic vagotomy with a drainage procedure, preferably gastroenterostomy. Excellent results have been reported. Grimson[3] states that in a group of one hundred and seventy-five patients, the percentage of satisfactory results was 91.3 per cent, moderately satisfactory results, 5.14 per cent, and definitely unsatisfactory results, 3.4 per cent. In Crile's[4] experience in one hundred and forty patients followed two to four years after vagotomy and gastroenterostomy for duodenal ulcer, 90 per cent have had satisfactory results, 3 per cent are improved, and 7 per cent are classified as failures. The incidence of demonstrable recurrent ulceration was 4.4 per cent.

We have always advocated gastroenterostomy (combining it since 1946, if possible, with infradiaphragmatic vagotomy) in poor risk patients who probably would not stand the extensive surgery demanded by gastric resection. This group includes those who are extremely obese, and many who have severe diabetes or hypertensive cardiovascular disease, as well as some patients over sixty-five years of age, and a few in whom it is felt that for technical reasons, the closure of the duodenum might present unusual hazards.

Since 1946, ninety-eight patients were subjected to gastroenterostomy, and in sixty-nine, vagotomy was added. There were four deaths, due in two to peritonitis, in one to cardiac failure and uremia, and in the fourth to coronary thrombosis. The appreciable mortality following this simple procedure was due to the fact that these patients were primarily poor operative risks. The follow-up on fifty-five cases of gastroenterostomy with vagotomy followed from eight months to six years,

shows forty-six well, four improved, three possible recurrences, and two proven recurrences. In twenty-nine cases of gastroenterostomy alone, there was one proven recurrence.

Subtotal gastrectomy with and without vagotomy for duodenal ulcer still remains our procedure of choice. From January 1, 1946, to January 1, 1952, in a series of 385 consecutive gastrectomies for duodenal ulcer, vagotomy was added in 165 cases. We have combined infradiaphragmatic vagotomy with subtotal gastrectomy, especially in patients who bled with and without pain, and those in whom the preoperative secretion studies showed an unusually high HCL, two categories of cases in which recurrences are most likely. We were interested to determine whether the addition of vagotomy would affect the immediate mortality and morbidity, and whether the combination of procedures would diminish recurrent ulceration. We divided these patients into two groups; group 1, those treated by subtotal gastrectomy, and group 2, those treated by subtotal gastrectomy with infradiaphragmatic vagotomy.

Approximately one-third of the patients in each group had had one or more episodes of severe bleeding, and a little less than 10 per cent of the patients had had a previous perforation.

Operation was performed whenever possible under spinal anesthesia, supplemented, if necessary, by either inhalation or intravenous anesthetic agents. Through a median epigastric incision, a bilateral infradiaphragmatic vagotomy was first performed. Then two-thirds to three-quarters of the stomach was resected restoring gastrointestinal continuity by an antecolic Hofmeister termino-lateral gastrojejunostomy. The pylorus was removed in all cases.* The duodenal ulcer was excised whenever possible, but there was never any hesitancy in leaving the ulcer in situ if its removal portended possible damage to the pancreas, or injury to the common bile duct. Permitting the ulcer to remain bears no direct relationship to the subsequent gastrojejunal ulcer since in the nine cases in this series in which there was subsequent recurrence, an active ulcer or healed scar was present in all resected specimens. If the duodenal closure was difficult, and dehiscence envisioned as a possibility, the stump was freely drained. In those eleven cases in which a duodenal fistula developed, the secretions were aspirated by continuous suction. Spon-

* There were two cases of prepyloric exclusion performed during this six year period which are not included in this series.

TABLE I—SUMMARY OF FOLLOW-UP RESULTS
(3 mos. to over 6 years)

Group 1 (S.T.G.) (216 of 220 patients)		*Group 2* (S.T.G. and I.D.V.) (161 of 165 patients)
SATISFACTORY RESULTS		
191	Well	146*
13	Improved	11
204 (94%)	Well or Improved	157 (96%)*
UNSATISFACTORY RESULTS		
1	Unclassified	4
(Pain—Negative X-rays)		3 Pain or vomiting or dumping (X-rays negative)
		1 Diarrhea
2	Suspected Recurrences	0
(a) Ulcer Type Pain (X-rays negative)		
(b) Mild Hemorrhage (RUQ Pain. X-rays and Gastroscopy negative)		
9	Proved Recurrences	0
SUBSEQUENT DEATHS*—(DUE TO UNRELATED CAUSES)		
1. Cause unknown. 10 mos. later. (Epileptic)		1. Homologous Serum Jaundice. (4 months later)
		1. Coronary Thrombosis 1 year later.

taneous closure eventually occurred in all.

The incidence of operative shock was negligible in both groups. Postoperatively after the combined operation (group 2), the incidence of pulmonary complications, gastric dilatation, vomiting and diarrhea was greater.

The mortality in this series of three hundred and eighty-five consecutive gastrectomies was 0.5 per cent. There were two deaths in which a postmortem examination disclosed a pulmonary embolism in one, and in the second, an acute pancreatitis involving the body and tail, complicated by hemorrhage, a colonic fistula and generalized peritonitis. The duodenal suture was competent. Both deaths occurred in group 2, but the addition of vagotomy did not contribute to the fatal outcome.

Follow-up results (Table I) obtained in all but six patients, ranged

TABLE II—TEST MEAL STUDIES — 1946 THROUGH 1951

Group 1 S.T.G.				*Group 2* S.T.G. and I.D.V.	
60/113	(53%)	anacid of tested	EARLY GRUEL or ALCOHOL	83/89	(93%) anacid of tested
33/42	(79%)	anacid of tested	LATE GRUEL or ALCOHOL (3 or more months)	30/30	(100%) anacid of tested
11/19	(58%)	anacid of tested	EARLY NIGHT	41/42	(98%) anacid of tested
27/77	(35%)	anacid of tested	EARLY HISTAMINE	76/115	(66%) anacid of tested
25/38	(66%)	anacid of tested	LATE HISTAMINE (3 or more months)	43/50	(86%) anacid of tested

from three months in a few to over six years in others. The majority of the patients are well and economically restored. However some have failed to gain weight. A minimal incidence of the dumping syndrome was seen in both groups. There was a change of bowel habit in group 2, which could be ascribed to vagotomy, and in about 10 per cent of these patients, there was a diarrhea which was disabling in only one case. Gross hemorrhage occurred in eight patients in the subtotal gastrectomy group, and in two of these, pain was also present. One patient complained of severe pain and x-ray revealed a jejunal ulcer. These nine are assumed to have had recurrent disease, ulceration or erosion. X-ray examination or operation confirmed the presence of a gastrojejunal ulcer in five. The percentage of recurrence in group 1 was 4.1 per cent. These failures are a challenge to surgery and present a difficult problem awaiting solution. There is a common denominator in all these recurrent cases, the presence of free HCL, the titre of which is usually high. Any patient with an ulcer diathesis who shows free HCL postoperatively, is a potential candidate for future ulceration. On the other hand, the presence of an achlorhydria is good insurance against further erosion or ulceration of the gastric or jejunal mucosa. Klein,[5] in 1929, in animal experiments, found that the incidence of achlorhydria following gastric resection, could be increased by partially eliminating the psychic phase of gastric secretion by adding anterior vagotomy. Cases of subtotal gastrectomy with partial anterior vagotomy, were subsequently reported substantiating his contention.[6]

It is interesting to note, in a comparison of test meal studies (Table II), that regardless of the test stimulant or the time after operation, gastrectomy combined with vagotomy produced a higher percentage of patients with achlorhydria than did gastrectomy alone. Moreover in group 2, there have been no recurrences to date. It would appear, therefore, that the increased incidence of achlorhydria following subtotal gastrectomy combined with vagotomy is directly related to the decreased incidence of recurrence.

In the collected series of duodenal ulcer reported by Jordan,[7] there was very little difference in the follow-up results of the resected cases when compared to those combined with vagotomy. It is probably for this reason that many surgeons performing gastrectomy, prefer to reserve vagotomy for those cases which later develop gastrojejunal ulceration.

Gastrojejunal ulceration, one of the most serious sequelae of surgery for duodenal ulcer, occurs in 15 per cent to 33 per cent of patients after gastroenterostomy, and in from 3 per cent to 8 per cent following subtotal gastrectomy. These patients invariably require corrective surgery in which the mortality is appreciable, the morbidity marked, and further recurrence not infrequent. A group of eighty-one cases was observed from 1940 to 1950; forty-two gastrojejunal ulcers followed gastroenterostomy (group 1) and thirty-one followed subtotal gastrectomy (group 2); and there were eight patients with gastrojejunocolic fistula, some of which have been previously reported.[8]

These patients had had duodenal ulcer disease from three months to thirty-six years prior to surgery, and the interval of good health between the primary operation and the first evidence of recurrence averaged 5.2 years, but varied between ten days and twenty-four years. The predominating symptom was usually epigastric pain, frequently associated with bleeding, but hemorrhage alone was the presenting symptom in four. The diagnosis was confirmed by x-ray in most cases, and test meals revealed exceedingly high values of free HCL. Many types of operative procedures were performed in these cases. The follow-up results based upon periodic personal examinations of the patients, cover one and a half to eleven years.

Twenty-nine patients who had a subtotal gastrectomy for gastrojejunal ulceration incident to gastroenterostomy, have been followed. Nine of these were combined with vagotomy. Twenty-three have remained well. These are given in Table III. Six of seven patients treated

TABLE III—RESULTS IN GASTROJEJUNAL ULCERS FOLLOWING GASTROENTEROSTOMY

Subtotal Gastrectomy 20 Cases	15 (75%) well 5 (25%) recurrences
Subtotal gastrectomy plus vagotomy 9 Cases	8 (89%) well 1 (11%) recurrence
Bilateral vagotomy alone 6 Cases	4 (67%) well 2 (33%) recurrences

TABLE IV—RESULTS IN GASTROJEJUNAL ULCERS FOLLOWING SUBTOTAL GASTRECTOMY

Resection of ulcer plus additional resection of stomach and jejunum 13 cases	9 (69%) well* 4 (31%) recurrence
Bilateral vagotomy alone 17 cases	10 (59%) well 7 (41%) recurrence

* Combined with infradiaphragmatic vagotomy in 4.

solely by vagotomy were followed from three to four and a half years. There were two recurrences. One was subsequently treated by subtotal gastrectomy and has remained well for three and a half years, and the other has refused further surgery.

These follow-up observations suggest that the best results in gastrojejunal ulcers following gastroenterostomy are offered by subtotal gastrectomy combined with bilateral vagotomy, reserving vagotomy alone for poor risk patients. However, even the combination of vagotomy and subtotal gastrectomy will not always give protection against further recurrence in these cases.

There were thirty-one patients with gastrojejunal ulcers following gastric resection (group 2). Many had had several antecedent procedures such as gastroenterostomy, vagotomy or jejunostomy. In sixteen of these patients, either because of a previous inadequate gastrectomy, or an obstructing ulcer involving the gastroenteric stoma, a further resection of the jejunum and stomach was necessary, and in four, this was combined with an infradiaphragmatic vagotomy. Of thirteen patients surviving a secondary gastric resection, nine have remained well, and four have developed recurrent ulcer (Table IV).

Bilateral supradiaphragmatic vagotomy as a solitary procedure was first performed by us in 1939 in two cases of jejunal ulcer following subtotal gastrectomy.[9] Since 1940, vagotomy was done on eighteen such patients, half by the transthoracic approach, and half by the abdominal route without mortality. All cases have been followed. One died three months after operation from an unknown cause. Ten have remained well or were markedly improved. Seven were failures. Four patients with active symptoms in whom the insulin test remained positive after bilateral vagotomy, were subjected to a second operation in a further attempt to divide the nerves completely. The subsequent insulin tests still remain positive. There were three patients whose general physical condition was considered so poor that a preliminary jejunostomy for alimentation was performed and later in two, definitive surgery was attempted. One had a vagotomy with a good result. The other was operated upon elsewhere and died postoperatively.

To recapitulate then, the best follow-up results would seem to have been obtained in those cases in which further gastric resection, when indicated, is combined with infradiaphragmatic vagotomy. However in the poor risk patient, vagotomy alone may be the only procedure which may be safely performed.

When group 1 and group 2 are compared, the poorer results obtained in gastrojejunal ulcers following subtotal gastrectomy, are striking. The reason for this may be ascribed to the fact that in group 1 the ulceration followed an inadequate primary operation, gastroenterostomy, whereas in group 2, even the more radical procedure, subtotal gastrectomy, did not protect against recurrence. These patients apparently must represent a more severe form of ulcer disease. In fact a few of them developed recurrence after recurrence despite a multiplicity of operations, including several gastric resections, vagotomy, or both combined, but in all there was always a persistence of free HCL in high concentration. Possibly this unusual type of case should be treated by total gastrectomy.

Gastric ulcer differs from duodenal ulcer in many respects. It is not as frequent, it occurs in an older age group, and it either may undergo carcinomatous transformation, or may be a carcinomatous ulcer primarily. As Palmer[10] has so tersely stated, "there are no diagnostic signs pathognomonic of benignancy; on the other hand there are definite criteria of malignancy." The clinical history, the x-ray findings, the gastroscopic appearance, and the fact that an ulcer seemingly disappears

under medical therapy, does not always eliminate the possibility of malignancy. Furthermore, in some instances, neither the surgeon at the time of operation, nor the pathologist from the macroscopic examination of the resected specimen, can be positive as to the nature of the lesion. For these reasons, if an iota of doubt exists as to the clinical diagnosis, the case should be explored rather than risk further medical treatment during which period, a so-called "ulcer" may progress to the stage of inoperable carcinoma.[11]

All surgeons now agree that subtotal gastrectomy with radical removal of the lesion is the only logical operation for gastric ulcer. From 1937 to 1952, subtotal gastrectomy was performed for gastric ulcer in one hundred and eighty-six patients There were seven deaths (3.7 per cent). The follow-up results of resection for benign ulcer are excellent, and recurrences of either gastric or gastrojejunal ulcer are negligible.

However, benign ulcers, juxta-esophageal in position, presented a special problem. They should be approached with caution because a resection here would invariably imply either a total or an esophagogastrectomy. These operations have an appreciable mortality and immediate postoperative morbidity. And symptoms may develop later due either to stenosis at the point of anastomosis, or to a dilated atonic stomach secondary to complete vagotomy. For ulcers of this type, provided there is every good reason to believe they were benign, and we have not been infallible in our judgment, a Madelener procedure has been performed. This is a palliative gastrectomy in which the stomach is resected distal to the ulcer which remains. With the invariable development of a postoperative achlorhydria, the ulcer heals and the symptoms disappear. This procedure was performed in seventeen cases, most of whom were poor risk patients. There was one death in a patient with a bleeding shallow ulcer in which hemorrhage persisted, and another death on the second postoperative day from a cardiac complication. In two, although the ulcer disappeared by x-ray, and a period of well being ensued, carcinoma became evident in one after three years, and in the other after four years, both inoperable at the time of the second exploration. In the last patient who died postoperatively, and in whom a postmortem examination was obtained, the pathologist felt that the original benign lesion was not related to the carcinoma. On the other hand, in two other patients, a total gastrectomy was successfully performed for

large cardiac lesions which at the time of operation were thought to be malignant, but were proven to be benign on pathologic examination.

In conclusion, we believe at present that subtotal gastrectomy with vagotomy in duodenal ulcer gives excellent clinical results and offers the best insurance against recurrence. Gastroenterostomy preferably with vagotomy has a distinct place in the treatment of the poor risk patient. Patients who develop gastrojejunal ulceration following gastroenterostomy should be treated preferably by subtotal gastrectomy with vagotomy. Cases with ulceration following subtotal gastrectomy should be treated by further gastrectomy, if previously inadequate, but in all instances by infradiaphragmatic vagotomy. Gastric ulcers should always be treated by subtotal gastrectomy except in a juxta-esophageal ulcer in which palliative gastrectomy may be indicated.

However, in the evaluation of any method of therapy for duodenal or jejunal ulcer, one must bear in mind that once a patient has developed a lesion, there is always the potentiality for recurrence regardless of the type of therapy used. Recurrent ulcers have been reported thirty years after corrective surgery so that any definitive statement as to the permanent effect of any given therapeutic measure based upon the results of short term follow-up observation should be viewed with extreme caution.

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AFFECTIONS OF THE FACIAL NERVE*

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THE facial nerve is a mixed cranial nerve just as are the trigeminal, glossopharyngeal and vagus and, in common with these, it presents symptoms which are characteristic of the motor or sensory component involved. The motor component of the facial nerve is of greater importance since the facial expression of an individual is dependent upon its integrity. Everyone is aware of the distress which a patient with unilateral paralysis of the face experiences, but we also should realize that there are other affections of this nerve which may, on occasion, be even more distressing.[1]

Anomalies of the facial nerve with respect to its course through the temporal bone apparently are rarely encountered for the otologic and anatomic literature is almost barren of reported instances of such deviations. I see no reason, however, why deviations in the course of this nerve should not be expected. If anomalous development can occur elsewhere in the body there is no logical reason to assume that the facial nerve should be exempt.

Barnhill[2] stated that Behrens found in cadaver material a facial nerve that "passed outward to the surface in such a position that, had the individual suffered from a mastoid abscess, injury would have been inflicted upon the nerve even in the hands of the best operator, since in this instance, it passed directly through a part of the field always used in making the surgical approach." Hawley,[3] in 300 dissections, found the vertical segment of the facial nerve displaced posteriorly 3 or 4 mm. from its usual plane in four instances. Kettel[4] has reported seven instances in which this portion of the facial nerve pursued an abnormal course in 125 operations upon the facial nerve. House[5] has found the facial nerve coming over the top of the horizontal semicircular canal on two occasions, one in a cadaver and the other in a patient upon whom he had

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intended to do a fenestration. Both Maxwell[6] and Kinney[7] have encountered a single instance in which the facial nerve was misplaced in patients with congenital maldevelopment of the ears. I have one patient upon whom I performed a radical mastoidectomy in whom the facial nerve was situated about 1 mm. more laterally than the most prominent point on the convexity of the osseous horizontal semicircular canal. In all other respects the development of the temporal bone of this patient apparently was normal.

It seems quite possible to me that minor deviations from the normal course of the facial nerve occur more frequently than a review of the literature would indicate. Only in relatively recent years have the training of the otologic surgeon and the surgical technique necessary for adequate temporal bone surgery been augmented to the point that the operator now knows where the facial nerve normally should lie. Until then the surgeon approached the vicinity of the facial nerve with a great deal of trepidation and provocation and, as a result, was in no position to observe minor deviations of this nature.

Disturbances of the sensory portion of the facial nerve are not common and are manifested by pain in and about the ear. In their milder form they not infrequently cause the patient considerable distress because of the persistent, aching type of pain which wears an individual down just as does a toothache. The pain in the more severe type is intense and causes the patient to seek early relief by consultation with a physician. Pain of this nature may be localized deep within the ear without radiation to adjacent structures or in and about the ear with radiation to the face, pharynx or tongue. The last distribution frequently is associated with herpetic lesions of the external ear and paralysis of the face and is commonly designated as Hunt's syndrome.

This syndrome has become so well known since James Ramsay Hunt[8-10] reported the result of his investigations in 1907 that there is no need to examine it further in this discussion. Suffice it to say, that while there is contention that the geniculate ganglion is not the site of the lesion as maintained by Hunt, this condition does exist as a clinical entity and its pathogenesis and treatment remain unsolved.

Although herpes zoster oticus is a painful affliction, it does not compare in severity with the pain experienced by a patient suffering from geniculate neuralgia. Since the geniculate ganglion is presumed to be the ganglion and the nerve of Wrisberg the sensory root for the sensory

component of the facial nerve, this disorder is sometimes spoken of as tic douloureux of the nervus intermedius. Clark and Taylor[11] reported a case in 1909 in which the patient required 12 grains of morphine daily to obtain relief from the pain. The pain usually occurs in paroxysms just as does typical tic douloureux of the trigeminal nerve with which it has been confused. It is intense, located deep within the ear and usually does not radiate until the disease has been present for some time. There are no associated herpetic lesions or neurologic signs such as are encountered with herpes zoster oticus. As the duration of the disease progresses, radiation of pain to the face, periauricular area and neck does occur but is not as severe in these locations as it is deep within the ear. Occasionally, a minute trigger zone can be demonstrated on the posterior superior wall of the external auditory canal just lateral to the annulus of the tympanic membrane.

Geniculate neuralgia is a rare condition and its etiology is unknown just as is the etiology of idiopathic neuralgia of the trigeminal or glossopharyngeal nerves. From personal experience, however, I know that an osteitis about the geniculate ganglion secondary to chronic suppurative otitis media can produce pain of this nature for I have performed a radical mastoidectomy and exposed the geniculate ganglion in one patient presenting this symptomatology and complete relief of the pain was obtained.

When there is radiation to the face, the pain of geniculate neuralgia may be confused with that of trigeminal neuralgia. However, the differential diagnosis should not be difficult if it is remembered that the primary site of the most intense pain is localized deep within the ear in geniculate neuralgia in contradistinction to the face, eye or lower jaw as is the case in trigeminal neuralgia. Glossopharyngeal neuralgia may cause pain in the ear in conjunction with that in the throat but the pain produced by neuralgia of the geniculate ganglion is never referred to the pharynx or posterior third of the tongue. In addition, trigger areas frequently are present on the face or in the mouth when the pain is due to trigeminal neuralgia or, in glossopharyngeal neuralgia, on the posterior third of the tongue or pharyngeal wall. These trigger areas serve to initiate the painful attack on washing the face, brushing the teeth, chewing or swallowing.

Medical treatment is usually ineffectual in either relieving or preventing the attacks of pain. We routinely employ a so-called "neuralgia

regimen" which consists of a mild sedative, thiamine chloride 10 mg., nicotinic acid 50 mg. and ferrous carbonate 1 gm. three times daily in all cases of typical or atypical facial neuralgia and this may be helpful in diminishing the intensity and the frequency of the paroxysms of pain in this condition. However, permanent and complete relief can be obtained through intracranial section of the nervus intermedius.[12] Three of the four patients whom we have encountered and the three cases that have been reported in the literature since 1909 have obtained complete and permanent relief from their symptoms by intracranial section of the nervus intermedius.

Disturbances of the motor division of the facial nerve are manifested by paralysis, twitching or spasm of the muscles concerned with facial expression. Paralysis of the posterior belly of the digastric, stylohyoid and stapedius muscles, which also receive their nerve supply from the facial nerve, produces such insignificant symptoms that there is no need to consider them in this discussion. Facial paralysis is the most important disorder of the facial nerve. Lacerations of the face, surgical intervention on the parotid gland, mastoid process or acoustic nerve, fractures of the skull, acute or chronic suppurative otitis media, labyrinthitis or petrositis, malignant disease or cholesteatoma of the temporal bone, intracranial lesions, tumor of the facial nerve, Bell's palsy, herpes zoster oticus, birth injury or congenital maldevelopment all may result in paralysis of the facial nerve.

Paralysis of the face may be either central or peripheral in origin. As the former is only of interest because it aids in the location of an intracranial lesion its elucidation is not pertinent to a discussion of this nature.

When facial paralysis is noted at or shortly after birth it is considered to be of congenital origin.[13, 14] It occurs as a result of obstetric injury or disorders of embryologic development and its prognosis is dependent upon the factors which produced the palsy. Facial paralysis caused by trauma to the extracranial portion of the seventh cranial nerve during forceps deliveries is usually unilateral and is the result of direct trauma to the nerve after its emergence from the stylomastoid foramen by the blade of the forceps or by indirect pressure from edema or extravasation of blood into the injured soft parts surrounding the nerve. Rarely, the paralysis may be of the central type as a result of trauma to the facial area in the cortex or of hemorrhage involving the upper neuron.

Unilateral facial paralysis may also occur because of injury to the

facial nerve as a result of inherent pressure factors during pregnancy and labor. Facial paralysis occurring during the latter months of pregnancy caused by the head being pressed against the shoulder is associated with cranial and facial asymmetry. This occurs in cases in which the intrauterine pressure is greater than usual such as might be found in first pregnancies with large babies or in multiple pregnancies. Protracted labor with large babies, contracted pelves or both may cause peripheral facial paralysis as a result of pressure upon the facial nerve by the sacral promontory or other bony prominences of the birth canal. A central type of palsy secondary to a depressed fracture of the skull impinging upon the facial area of the motor cortex or to hemorrhage in this region may occur in a similar manner.

Facial paralysis caused by embryologic maldevelopment is rare. The majority of such cases are bilateral and, because of the close proximity of the nuclei of the sixth and seventh cranial nerves, there is almost invariably an associated abducens palsy. In addition, various combinations of developmental defects may accompany these diplegias such as paresis or paralysis of the oculomotor, motor trigeminal, glossopharyngeal and hypoglossal nerves, clubfoot and malformation of the upper extremity and chest. Occasional cases presenting unilateral facial paralysis without other associated cranial palsies have been reported. The paralysis of the face is usually complete but when incomplete, the superior group of muscles is more severely affected. The etiology is obscure although there is a suggestion that the formation of an excessive amount of cerebrospinal fluid may be the explanation. Histopathologic study of four cases has revealed that nuclear hypoplasia accounts for the cranial nerve palsies in all typical cases of the syndrome.

There is no specific treatment for congenital facial paralysis. The prognosis for spontaneous recovery from the palsy in those cases due to obstetric causes is influenced by the manner in which the injury to the nerve has occurred. Thus, the prognosis for spontaneous recovery from facial paralysis of the peripheral type is good in those cases in which the injury to the nerve follows pressure from the application of obstetric forceps or impingement upon a bony prominence of the birth canal during labor. However, when the palsy produced by these factors is of the central type or when the paralysis occurs as a result of the head being pressed against the shoulder during the latter months of pregnancy, the prognosis is not so favorable. The prognosis for improve-

ment in facial paralysis when it is the result of embryologic maldevelopment is poor.

One of the most controversial enigmas of modern medicine is Bell's palsy. The etiology of this condition remains a conjecture although the modus operandi of the production of the palsy appears to be reaching a state of equilibrium. Kettel,[15] Sullivan[16] and Hilger[17] agree that the paralysis of the nerve is initiated by a disturbance in the blood supply of the nerve producing an ischemia but do not agree on the significance of the edematous neuropathy which follows. Kettel and Hilger believe that it is the edema itself which produces the paralysis of the nerve, while Sullivan thinks that the paralysis is the result of pressure upon the nerve from the edema.

Difference of opinion also exists as to the proper management of this affection of the facial nerve. It has been loosely estimated that between 75 and 85 per cent of these patients spontaneously recover from the palsy. As a result treatment has been directed more toward symptomatic and psychologic relief than toward correcting the pathologic process which is thought to be the cause of the paralysis. At the present time treatment appears to vary between doing nothing at all to surgical intervention in every case exhibiting a negative faradic test.

Electrical stimulation of the face is the most common and, to my mind, the most useless single form of treatment employed since it has absolutely no therapeutic effect upon the paralysis of the nerve. The administration of vasodilator drugs such as niacin by mouth or procaine hydrochloride intravenously in an effort to relieve the ischemia of the facial nerve is currently popular. Procaine hydrochloride in a dosage of 4 mg. per kilogram of body weight to a liter of distilled water may be of benefit when administered early in the course of Bell's palsy but it has the disadvantage that it can neither be utilized as a routine method of office treatment nor be economically used for prolonged treatment. Although niacin, 50 to 100 mg. four times a day, may not be as efficacious in relieving the vasospasm, it has the advantage that it can be used in an ambulatory patient over a long period. It would seem that administration of a combination of a vasodilator drug and procaine hydrochloride intravenously early in the course of the disease, supplemented by niacin by mouth for prolonged effect, would offer the best prognosis for resolution of the reversible changes produced in the nerve by the disturbance of circulation. When the patient is seen late and it is certain

that axonal degeneration has occurred, perhaps surgical intervention would be of help in re-establishing the circulation and permit more rapid recovery from the palsy.

Kettel,[15] Cawthorne[18] and Sullivan[16] are proponents of decompressing the facial nerve in an effort to cure Bell's palsy. Cawthorne and Sullivan believe that when the palsy is complete and the nerve does not respond to faradic current, decompression of the facial nerve is advisable in order to give the patient every opportunity to obtain complete recovery from the palsy. Kettel, on the other hand, does not rely upon the faradic test and advises decompression in those patients in whom signs of beginning mobility have not appeared after an observation period of two months. Furthermore, he advises decompression of the facial nerve if spontaneous recovery becomes arrested before complete restitution has occurred. A more conservative attitude is taken by Hilger who holds that as long as the opportunity for spontaneous recovery is not being jeopardized by waiting, surgical intervention seems contraindicated. It would be difficult to select which patient required decompression of the nerve on the basis of any information we might be able to obtain thus far. If this procedure is to be effective it should be instituted before degeneration has occurred and, therefore, while the faradic response is still present. Perhaps if there were some way to determine which case of Bell's palsy was ultimately to lose the faradic response, decompression of the facial nerve for this condition could be placed on a much sounder basis and in a more logical position. Until this is possible, however, it appears that whether or not the facial nerve in a case of Bell's palsy should be decompressed will depend upon the surgeon's personal criteria.

Melkersson's syndrome[19] is featured by chronic lymphedema of the face, particularly of the upper lip, in association with a concurrent or antecedent homolateral paralysis of the facial nerve. The paralysis of the face frequently is recurrent. The pathogenesis is assumed to be identical to that of Bell's palsy, and, therefore, the treatment of the paralysis of the face is of a similar vein. Roentgen therapy or plastic surgery may be utilized to correct the chronic lymphedematous state of the face or lip.

Traumatic facial paralysis as a result of mishap in otologic surgery is not encountered commonly in the practice of otolaryngology today. Nevertheless, injuries to the facial nerve still occur. Although facial

palsy following surgical intervention upon the mastoid process has largely been eliminated, it has increased due to other causes. Some of these are the result of progress in our civilization. Trauma to the facial nerve following surgical procedures for the extirpation of neoplasms of the brain, parotid gland or face and automobile accidents with severe lacerations of the face or fracture of the skull are more prevalent today than a generation ago. Furthermore, as long as man wields a knife or uses a gun in combat, facial paralysis will be with us. It has definitely increased as a result of the nature of modern warfare.

The ultimate goal of surgical procedures upon the facial nerve is the physiologic restoration of its function. Operations, such as decompression, end-to-end suture, nerve grafting or anastomosis of the distal stump of the facial nerve to the central end of an adjacent cranial nerve, effect this result in the majority of cases. With respect to the last procedure it is my opinion that hypoglossofacial anastomosis is preferable to spinofacial anastomosis.[20]

When facial paralysis fails to be benefited by any of these procedures or they are not applicable, either because the distal branches of the nerve cannot be found owing to antecedent surgery on the parotid area or when facial paralysis has existed for such a period of time that atrophy of the facial musculature has occurred, improvement in the unsightly deformity of the face can be obtained only by plastic surgery. This may consist of either the transplantation of pedicled strips of adjacent muscle innervated by the fifth cranial nerve or mechanical support of the paralyzed side of the face. I have not had experience with the former. Stainless steel or tantalum wire and mesh, animal tendon and autogenous fascia lata have been utilized to support the face mechanically. When the support is to be permanent, none give as good a result as do slings of autogenous fascia lata.

A description of the techniques involved in the performance of these operative procedures is not pertinent to this discussion. I should like to emphasize, however, that those procedures which re-establish the anatomic continuity of the facial nerve are as applicable to lesions of this nerve situated in the parotid gland and face as they are to those within the mastoid and middle ear. For some reason the impression is prevalent that a defect in the facial nerve situated in the parotid area or face is not amenable to surgical correction. This is not true. End-to-end suture or nerve grafts will restore the function of the facial nerve

in such situations as well as in those located within the mastoid and middle ear. Surgeons who either accidentally or intentionally injure the facial nerve during an operation in this region should be conscious of the fact that the ensuing paralysis of the face usually can best be relieved by the employment of these methods of nerve repair.[21]

The improvement in the paralysis of the face which will be obtained varies with the accuracy of the assessment of the facial paralysis and the surgical procedure employed, and between patients in whom identical measures have been used. For this reason, the surgeon should not be too optimistic in his description of what can be accomplished by treatment, for what will be satisfactory to one patient may not be to another. In general, best results are obtained with those operations which permit restoration of the anatomic and physiologic continuity of the facial nerve. Thus, whenever possible, decompression, end-to-end suture and nerve grafting should be employed to obtain improvement in facial palsy.

Paroxysmal hemifacial spasm is the opposite of facial paralysis. In the majority of patients it is a minor, though distressing, neurologic disease. When severe, however, it causes such a grotesque appearance of the face that the psychologic and economic adjustment of the patient may be so seriously interfered with that almost any penalty is considered worth the price for relief. Rarely, hemifacial spasm may be bilateral and when severe, these patients are often almost completely disabled because of the clonic contractures about the eyes and mouth which may seriously interfere with vision, speech and eating.

The etiology is unknown.[22] Harris[23] believed that it is due to a degenerative lesion of the facial nerve at or below the geniculate ganglion. In support of this view is the not infrequent appearance of clonic spasm of the muscles of the face following recovery from facial paralysis, the associated facial weakness and contracture in long-standing cases of this condition and the observation of Williams[24] that there is evidence of compression of the facial nerve near the stylomastoid foramen in patients upon whom he has operated. The spasm is clonic in nature, involves the eyelids first, and usually progressively spreads to adjacent muscles until all muscles supplied by the facial nerve may be involved. The paroxysms are aggravated by emotional stress, fatigue and voluntary movement of the face.

Treatment has run the gamut of man's imagination.[25] Medical treat-

ment is of no avail except perhaps in the most minor instances in which mild sedation may be beneficial in minimizing the influence of extraneous aggravating factors. The greatest benefit from treatment has been obtained with those measures that result in paralysis of a portion or all of the facial nerve. This formerly was accomplished by the injection of alcohol into the nerve but has since largely been abandoned in favor of section of the nerve. The spasm usually recurs if regeneration of the nerve is permitted and, therefore, Coleman[26] has suggested that when the spasm is chiefly confined to the orbicularis oculi, the branch of the facial nerve to this muscle be sectioned and the proximal segment be redirected in order to prevent reneurotization of the distal portion. When unilateral involvement of all of the muscles is severe Coleman advocated hypoglossofacial anastomosis in order to prevent recurrence of the hemifacial spasm and permanent paralysis of the face. We have employed selective section of the peripheral branches of the facial nerve, with excellent result. A faradic nerve stimulator applied directly to the exposed branches permits selection of the branch of the facial nerve producing the spasm in the involved region without indiscriminate sacrifice of other branches not directly concerned with its production. In no case has the resulting paralysis been obviously noticeable.

Williams has recently advocated decompression of the facial nerve in order to relieve the spasm of the face. He has operated on nine patients, with temporary facial paralysis occurring in all but two patients and alleviation of the hemifacial spasm in all patients. His first patient, however, who was operated on fifteen months ago, is beginning to show slight return of the spasm. It is my belief that the relief which his patients have obtained was the result of the injury incurred by the facial nerve during the decompression rather than of relieving the compression of the nerve at the stylomastoid foramen. I anticipate that the majority, if not all, of these patients will have a recurrence of the hemifacial spasm, although it may be improved. This improvement may be sufficient to ultimately justify considering this surgical procedure as the treatment of choice since permanent paralysis of the face would be eliminated. Certainly, it would seem that there is sufficient evidence that this operation is beneficial to warrant decompression of the facial nerve in a sufficient number of cases of this nature so that its correct status can be established.

Tumors of the facial nerve are rare.[27, 28] The tumors which have

been reported in the literature are benign. They arise from the fibrous tissue elements concerned with the structure of a nerve and are rather loosely differentiated as neurinomas when their origin is from the Schwann cells and as neurofibromas when they arise from the interstitial fibrous tissue or nerve sheath of the nerve. For the purpose of this brief discussion, however, they can be considered as being of common identity since their symptomatology and treatment are alike although disagreement exists among pathologists as to their differentiation.

The majority of these neoplasms of the facial nerve occur within the fallopian canal, although they may occur anywhere in the peripheral distribution of the facial nerve.[29, 30] When they occur within the temporal bone, their initial symptom usually is the appearance of a slowly progressive facial paralysis; when they appear in the face or parotid gland, the most prominent feature is, most commonly, solitary tumor formation without paralysis of the face. Tumors of this nature are not invasive but cause local destruction of tissue by increase in size. Because their growth is slow many months may elapse following the appearance of the facial paralysis before a positive diagnosis can be established by biopsy of neoplastic tissue which either has perforated the tympanic membrane to appear in the external auditory canal or has eroded through the osseous external auditory canal. On rare occasions, the tumor may be suspect because of changes within the middle ear as seen through the intact tympanic membrane and a positive diagnosis is established either by biopsy through a myringotomy opening or by exploratory operation.

The treatment is adequate surgical excision of the tumor regardless of its location. The facial paralysis can then be relieved either by repairing the defect in the facial nerve with a nerve graft or, when the central end is inaccessible, by anastomosis of the distal stump of the facial nerve with the hypoglossal or spinal accessory nerve. I have had two such patients in whom satisfactory relief from the paralysis of the face has been obtained with these methods of treating traumatic facial paralysis.

Summary

A brief discussion of the various disturbances of the facial nerve has been given. Affections of the facial nerve are manifested, most commonly, by pain in or about the ear or by paralysis of the muscles of facial expression, depending upon whether its sensory or motor component is affected by the pathologic process. Affections of the sensory

portion are rare. When present they cause the patient great distress and, in the case of geniculate neuralgia, tax the diagnostic acumen of the physician.

Disturbances of the motor component are more common. The grotesquerie of facial expression which a patient with unilateral paralysis of the face presents is familiar to us all. The management of traumatic facial paralysis, when the injury to the facial nerve is confined to the temporal bone, has been established. It should be emphasized, moreover, that these methods of treatment are as effective in relieving facial paralysis occurring as a result of injury to the facial nerve in the region of the parotid gland or face as they are within the mastoid or middle ear. The etiology and treatment of Bell's palsy is still in a state of flux.

Still another disorder of the motor component is hemifacial spasm. This condition is diametrically opposed to paralysis of the face and may cause a patient even greater psychologic and economic distress than does the latter. It should be realized that it is not a psychic disturbance and that prompt institution of effective treatment will rehabilitate a patient so afflicted.

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BACTERIAL RESISTANCE AS A FACTOR IN ANTIBIOTIC THERAPY*

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THE possibility that bacterial resistance may be important as a factor in antibiotic therapy looms widely in the minds of American physicians today. That this is a fact, can be demonstrated by the enormous demand that is currently being made upon diagnostic bacteriological laboratories for tests for "sensitivity" of micro-organisms which are isolated from infectious processes to the various antibiotics which are used as therapeutic agents. In one general hospital with which the author is well acquainted, between three and four hundred tests for "sensitivity" are requested each week. It is obvious that such a demand is bound to throw an additional burden on already overworked bacteriological laboratories, and also, *it increases the cost of patient care.* An important question is the necessity of doing such tests as routine measures. What is their real value, if any, and are physicians falling into another grievous and expensive error in substituting laboratory tests for sound clinical knowledge and judgment? One cannot answer these questions without discussing the factors concerning the current status of the "sensitivity" of bacteria to antibiotics, or conversely, their resistance to such agents. Unless a physician has an understanding of this problem, he will continue to overburden the laboratory with "sensitivity" tests, thereby increasing the costs of medical care, and often, with little real benefit to the patient.

THE NATURE OF BACTERIAL RESISTANCE

It is believed that bacteria are or may become resistant to the antibacterial effects of antibiotics because:

1. They may produce during growth a substance which antagonizes

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the antibacterial effect of an antibiotic. This type of insensitivity to antibiotics has been termed "natural" resistance. It best can be illustrated by those species of micro-organisms which are resistant to the antibacterial effects of penicillin because they produce penicillinase, an enzyme which inactivates penicillin.

2. As a possible result of a direct effect of an antibiotic, previously "sensitive" bacteria become adapted, i.e., resistant to the antibacterial effects of an antibiotic.

3. In any given bacterial population which is producing an infection, individual cells arise by spontaneous mutation which are resistant to the antibacterial effects of the antibiotic agent which is being used as the therapeutic agent. These cells being resistant, multiply freely, and soon make up the total population in the infectious process. An exaggeration of this phenomenon is when in a single mutation, the bacterial cell not only becomes resistant, but actually dependent on the presence of the antibiotic for further growth. This latter type of mutation has been ably described by Miller and Bohnhoff, and other observers.[1-6]

The Clinical Aspects of Bacterial Resistance

Facts and theories of the nature of bacterial resistance to antibiotics have been outlined briefly above. How they apply currently will be discussed in relation to the five antibiotics which are most commonly used for the systemic treatment of infections.

1. *Penicillin:* Although it is possible to produce in vitro, mutants of various micro-organisms which are resistant to the antibacterial effects of penicillin, the physician's chief problem in penicillin therapy results from strains of bacteria possessing "natural" resistance. This is particularly true as far as the treatment of patients infected with pathogenic strains of Staphylococcus aureus are concerned, because in the last ten years, those strains which form penicillinase, have become dominant in producing infections. As early as 1949, Finland[7] reported that there had been a marked change in Boston in the sensitivity of pathogenic strains of Staphylococcus aureus to penicillin. In the period of 1941-46, slightly over 90 per cent of such strains had been sensitive in vitro to one unit of penicillin or less; between 1946 and 1949, less than 50 per cent of the strains of staphylococci isolated from infectious processes had a similar degree of sensitivity, and at least a quarter of the strains were resistant to 15 units or more of penicillin. Finland's findings have been widely

confirmed. This phenomenon is the result of the killing off, or suppression of the spread of sensitive strains, thus permitting the resistant pathogenic strains to diffuse freely. *The fact that the majority of strains of disease-producing staphylococci are resistant to the antibacterial effects of penicillin should be borne in mind by all physicians.*

The development of resistance to penicillin as the result of bacterial mutation has been firmly established in certain cases of subacute bacterial endocarditis[8-10] and in other varieties of bacteremia or septicemia[9, 11-13] However, the development of this type of resistance must be a very rare happening, and of little significance, when compared with the millions of infections treated with penicillin, and in which the infecting micro-organism did not become resistant. *From a practical point of view, the physician can assume that resistance to penicillin resulting from bacterial mutation or adaptation is very rarely of clinical importance.* It is only the naturally resistant, penicillinase-producing strains that may give him trouble.

2. *Streptomycin or Dihydrostreptomycin:* Here the situation respecting resistance is quite different. It may even be said to be unique among currently used antibiotics. Early in the clinical use of streptomycin for the treatment of urinary tract infections[14-16] it was noted that resistant strains of the infecting organism emerged frequently. This was subsequently observed in relation to a number of other infections including tuberculosis. While the loss of sensitivity may occur slowly in a bacterial population exposed to streptomycin this is not always the case. Often resistance to the antibacterial effects of streptomycin develop very rapidly. Even more astounding is the fact first observed by Miller and Bohnhoff,[1, 2] that micro-organisms may rapidly become dependent on streptomycin as a growth factor. This, these observers also demonstrated in patients who were being treated with streptomycin.[17]

It has been shown, both for mutants, resistant to streptomycin, which were produced in vitro, and also for those initially isolated from infectious processes, that the highly resistant strains were quite stable and preserved this characteristic. As a result of this phenomenon, these highly resistant mutants have replaced the strains of bacteria which were sensitive to streptomycin, as pathogenic disease agents. Thus in many infections in which streptomycin was formerly very effective, it is without effect today. Even in those infectious diseases (other than tuberculosis) in which the infecting bacteria are initially sensitive to streptomycin, the

chances are that within 48 to 96 hours, they will be resistant to this antibiotic. These findings prompt the following recommendations: *that in the United States, streptomycin be used only for the treatment of tuberculosis, unless adequate technical facilities are available for controlling therapy by the accurate determination of the sensitivity of the infecting organism to the antibacterial effects of this antibiotic.*

3. *Aureomycin, Chloramphenicol and Terramycin:* Natural resistance on the part of bacteria, i.e., that produced by antagonistic substances, has not been demonstrated in relation to these three antibiotics. Resistance developing in a step-wise pattern has been described. It is rarely of high degree, generally being two-fold, four-fold or somewhat greater, and no reports are extant which indicate that bacteria may become dependent for growth on the presence of one of these antibiotics. It has also been noted that when certain bacteria acquire a degree of resistance to one of these antibiotics, they generally show a parallel, although lower acquisition of resistance to the other two antibiotics.[18] This seems to be almost always true for gram-negative bacilli, but it varies with individual strains of the gram-positive cocci. Another interesting observation which has been made in relation to these three antibiotics is that they have the ability to suppress (apparently permanently) penicillinase production by certain strains of micro-organisms which are "naturally" resistant to penicillin.[18]

Currently, it appears that resistance of micro-organisms to the antibacterial effects of Aureomycin, chloramphenicol and Terramycin is not a pressing problem. When anyone of these three antibiotics is employed it must be remembered, however, that if resistance develops, it will be parallel, with the possible exception of that to chloramphenicol, in infections produced by gram-positive bacteria. Hence, little will be achieved by shifting from one antibiotic to another within this group of agents. Furthermore, it must be borne in mind, that inasmuch as these antibiotics suppress the penicillinase mechanisms of certain bacteria which are "naturally" resistant to the antibacterial effects of penicillin, the possibility that this latter antibiotic may be employed in event of the failure of one of the three general purpose antibiotics must be kept in mind.

Testing for Sensitivity

The value of testing micro-organisms for their sensitivity to the various antibiotics, as a routine measure, prior to treatment, was questioned

earlier in this report. A careful study of the various factors involved in such testing has been made by Eleanor A. Bliss.[19]

Her observations indicate that the following factors may influence routine determinations of the sensitivity of micro-organisms to antibiotics.

1. Where the volume of work is great, errors may be made in the isolation and identification of the disease agent.

2. Variations in culture media influence the results of tests for sensitivity.

3. The state of the culture of bacteria under test, both in relation to its density and stage of growth is of considerable importance in such tests.

4. An improper understanding of the biological, physical and chemical properties of the antibiotic under test, in the varying culture media which may be employed in testing for sensitivity may produce an incorrect interpretation of the observed results.

It has been our contention for some time, that inasmuch as the factors which may influence tests for the "sensitivity" of micro-organisms to antibiotics are so variable, in general such tests could be disposed of, if physicians would only apply existing knowledge in their choice of antibiotics for the treatment of a given patient ill with an infectious process.

Bliss has tested this thesis with one hundred consecutive cultures of micro-organisms, obtained from a routine bacteriological laboratory on the original plates used for determining the "sensitivity" of these bacteria to antibiotics by the paper disc method. In this study she compared "guessing the sensitivity," i.e., on the basis of current knowledge, with the results obtained by the disc method of testing and those secured when the dilution tube technique was employed.

The results are interesting. To begin with, Bliss found an error of about 10 per cent due either to an improper identification of the culture or to the fact that it was "mixed." This is not surprising when one considers that the laboratory from which she received these cultures was doing hundreds of such tests a week, in addition to its regular work. Sixteen of the cultures were properly identified as Staphylococcus aureus. One would expect or "guess" that at least 50 per cent of these strains would be resistant to penicillin, i.e., producers of penicillinase, and that practically all of them would be "sensitive" to Aureomycin or

Terramycin. This was the case. With the disc method, the results with six strains were at variance with those obtained with the dilution tube technique. Nineteen strains of Staphylococcus albus were tested. One would expect most of them to be "sensitive" to penicillin in light of current knowledge. Using the dilution tube technique Bliss found that seventeen of the strains were "sensitive." However, when the disc method was used, but two strains could have been classed as "sensitive" to penicillin. This represented a marked discrepancy from both the "guess" and the results obtained with the dilution tube technique.

Twenty strains of coliform bacteria were subjected to comparative testing. One would have "guessed" that all would have been resistant to penicillin, about half of them to streptomycin, and that all would be "sensitive" to Aureomycin, chloramphenicol, or Terramycin. As was to be expected all were resistant to penicillin, five strains or 25 per cent were resistant to streptomycin, and three strains were resistant to Aureomycin and chloramphenicol when tested by the dilution tube technique. Thus, by "guessing" one would have been 85 per cent "right." The disc method again gave an erroneous impression, because the plates showed low values, especially for Terramycin. In the experience of Bliss, Terramycin rarely showed as much as "moderate" inhibition on the agar plates, even when the dilution tube technique revealed a high degree of activity.

Twenty-one strains of enterococci were tested. Fourteen were Streptococcus fecalis. One would expect most of these strains to be moderately "sensitive" to penicillin, Aureomycin, chloramphenicol and Terramycin, and resistant to streptomycin. This was the case when the tube dilution technique was used. With the disc method nine of the fourteen strains would have been listed as "insensitive." Seven of the strains of the enterococci produced beta hemolysis. All were resistant to streptomycin and all were as "sensitive" to penicillin as one would have expected. However, as against the "guess" that most of these strains of hemolytic enterococci would be "sensitive" to Aureomycin and Terramycin, five of the seven were found to be resistant to these two antibiotics. All were sensitive to chloramphenicol. Nine out of the ten strains of Proteus and three out of three strains of Pseudomonas aeruginosa were found to be resistant to all of the antibiotics studied. Three of seven strains of Streptococcus viridans were found to be moderately resistant to penicillin. These results were in line with what

would have been "guessed" in relation to their "sensitivity" to the various antibiotics.

In summary one can say that in the tests performed by Bliss, the "sensitivity" of the micro-organism to an antibiotic was properly estimated, prior to testing, about 80 per cent of the time. She has also demonstrated that the dilution tube technique has a degree of selectivity and sensitivity which is definitely greater than that of the disc method.

Conclusion

1. The physician has information available to him which should permit him to predict accurately in the majority of instances and without the assistance of the laboratory, the antibiotic to be used in the treatment of his patient.

2. Tests for the "sensitivity" of micro-organisms are subject to varying interpretations due to a number of factors such as, the method used, the state of the media and the organism under test, and errors in the isolation and identification of bacterial etiological agents.

3. Tests for the sensitivity of micro-organisms to antibiotics should be used when there is evidence that the original premise for the selection of an antibiotic for therapeutic purposes was incorrect, *and not as routine measures for selecting the antibiotic for therapy.*

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December 1952

December 4

5. TREATMENT OF CIRCULATORY FAILURE—ROUND TABLE—Chairman, Ludwig W. Eichna, *Associate Professor of Medicine, New York University College of Medicine*, with Doctors Mark D. Altschule, Stanley E. Bradley, Louis Leiter, and Eugene A. Stead, Jr.

CHRONIC LEUKEMIA: POLYCYTHEMIA VERA—Henry D. Diamond, *Associate Professor of Clinical Medicine, Cornell University Medical College.*

December 11

6. THE NEWER UNDERSTANDING OF GASTROINTESTINAL MOTOR DISTURBANCES AS A BASIS FOR IMPROVED THERAPY — Thomas P. Almy, *Associate Professor of Neoplastic Disease (Medicine), Cornell University Medical College.*

BRAIN AND SPINAL CORD TUMORS—Francis A. Echlin, *Associate Professor of Neuro-Surgery, New York University Post Graduate Medical School.*

(Continued on page 826)

SECRETORY OTITIS MEDIA*

With Classification Based On Amenability To Therapy

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CERTAINLY no subject in otolaryngology has attracted more attention within the last 6 to 7 years than a symptom complex known by various names—but more particularly as secretory otitis media or otitis media with effusion. At the A. M. A. meeting in Atlantic City, I presented an exhibit of ear drum photographs, among which were a series of secretory otitis cases. The ENT men that saw the exhibit were particularly interested in this series, and without exception stopped to discuss the therapy; many of them admitting that some of these cases were extremely baffling. This problem is plaguing us all. There is no question in my mind that the disease complex is much more commonly seen than previously. At the same time, the increased interest in this disease has resulted in many cases being diagnosed that were hitherto missed. My own interest in serous otitis dates back to my army career, where in a basic training center for air crew personnel, I examined the ears of great numbers of soldiers, and picked up about 100 cases of fluid in the middle ear; of which I reported results of studies of seventy-six cases.[1] Since then, many investigators have searched diligently for the answer to a disease that Gordon Hoople[2] so aptly calls "A Challenge to Otolaryngology."

In consideration of etiology, it has up to recently been generally conceded (and still is—by many investigators) that the basic pathologic cause of secretory otitis media is the blocked eustachian tube with the formation of either a transudate due to osmotic action of negative pressure acting on blood vessels of the tympanic cavity—or an exudate produced by a hypovirulent infection.

However, it is becoming more apparent that other factors independent of eustachian tube closure may play an important role in the

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formation of these effusions, and it is probable that in this etiologic realm we encounter the real problem of the recurrent secretory ear with the re-formation of fluid constantly or intermittently. It is in this latter classification that I am intrigued by Hilger's[3] conception of autonomic nervous system imbalance due to emotional stimuli or physical allergy (Williams'[4] so-called "pathergy") playing a part in certain forms of this condition so that we may be actually dealing with a vasomotor otitis media with a marked, continued, actively leaking mucous membrane involving the entire middle ear cavity including the mastoid and eustachian tube.

Allergic states have lately been considered an important culprit in the etiology of these cases—with extremes of opinion. Tobey[5] states that although the possibility of allergy as a cause of effusion has been constantly kept in mind in no instance has it proved to be an etiologic factor. Contrast this to Jordan's[6] consideration that out of one hundred and twenty-three patients, ninety-one or 74 per cent were definitely allergic.

Day[7] is convinced that in children most of the cases are allergic, especially to milk and orange juice. Only recently has it become recognized that secretory otitis media is an important problem in children, particularly because of its causation of deafness in childhood, reversible at this early age, but possibly the beginning of some of the irreversible adult hearing states.

The problem is particularly accentuated in that the child, of course, offers no complaints, as he is only presented to us by an observant teacher or parent, who suspects hearing loss in the child. It is alarming to consider how many of these cases never even reach the care of the general physician, much less the otologist. It is in this connection that we otologists have an important duty, i.e., to hammer incessantly at the general physician and the pediatrician, that, following an acute ear infection—however mild, even though normal temperature, relief of pain and alleviated parent anxiety seem to indicate resolution of the ear, the patient cannot be discharged until one of the cardinal signs of inflammation—"loss of function"—in this case the hearing, has returned to normal.

It is in this connection also that we may consider what may well be a prime etiologic factor. Are we modifying the virulence of ear infections with the antibiotics, so that instead of a purulent exudate, an

avirulent or hypovirulent infection causes a serous exudate? Has the use of antibiotics in general, bred an obtunded or attenuated series of organisms which, for the time being, is only capable of mildly insulting the tympanic mucous membrane? If we accept this hypothesis, we must believe with Tobey[5] that serous exudation and suppurative otitis media be considered sequential stages of the same process.

In children then, we must constantly be on guard to recognize symptoms of both the acute and the chronically obstructed eustachian tube with effusions in the middle ear. Lindsay and Perlman[8] have particularly emphasized the importance of diagnosis of the chronically obstructed eustachian tube.

The presence of hypertrophied adenoids or obstructive lymphoid remnants is certainly a positive indication for surgery when there is persistent serous otitis. I often aspirate both ears while doing a T & A and remove the fluid from the middle ear. Day[7] states that when he opens a serous or mucous ear in a child he always goes into the nasopharynx with his fingers to break up adhesions around the eustachian tube. As an aside, but very appropriate at this point, is my plea that we otolaryngologists learn to do an unhurried, more complete adenoidectomy, removing not only the posterior masses of adenoids, but also the many other masses of lymphoid tissue which are not touched by the standard adenoidectomy—particularly the infiltrated hyperplastic salpingo-palatine folds so often encountered (Furlong[9]).

The relationship between secretory otitis media and aero-otitis media has impressed many investigators, and as early as 1943 I attempted to draw an analogy between the two states. In both conditions, the drum head is retracted, the eustachian tube obstructed and fluid is present. It is my feeling that acute aero-otitis media can be considered as a sudden hyperacute secretory otitis by which the pathologic changes are caused by increased atmospheric pressure of descent acting on the eustachian tube in such a way as to literally "tear out" fluid, either serous fluid, serosanguinous fluid or actual blood from the blood vessels of the closed off tympanic cavity by intense negative pressure. In secretory otitis, the process is more gradual, with obstruction of the eustachian tube by mild inflammation and edema causing serous or mucoid secretion. In many cases, when aero-otitis does not resolve it may blend into what we recognize then as secretory otitis media.

Trauma may play a part in certain cases, for on several occasions I

have seen fluid formation following a blow across the ear.

The influence of the weather may be an important etiologic factor. In my Army cases, I noted that on the Gulf Coast where the military installation was located, we had an average of 10-20 per cent higher humidity than in the interior of the country.

Symptomatology

In the majority of cases, the symptom complex follows a fairly consistent pattern. The patient has, or recently has had, a nasal cold, sore throat, or some upper respiratory infection, or has been on a plane ride. One or both ears feel stuffy or blocked, and he generally complains bitterly of impaired hearing in the involved ear. Some of the terms used by patients to describe their feelings are: "ears feel dead or lifeless," "like a piece of wood," "stuffy," "blocked or hearing lopsided in that ear," or "feel something rolling in the ear like water," "feels like I am speaking through that ear." Tinnitus of various types may be complained of; and occasionally vertigo is present.

If only a small amount of fluid is present, hearing may be little or not at all affected. However, in most cases, deafness is markedly distressing and is the presenting symptom. It is this symptom of deafness which seems out of proportion to the length of time of symptoms, and to the apparent pathologic change that should lead one to suspect the diagnosis. Hearing loss as measured by the whispered voice, using 15/15 as normal may fall to as low as 1/15 or less, although usually the loss is about 6/15. When measured by the audiometer under ordinary clinic conditions, an average of 30 decibels of loss is found if the ear contains a great deal of fluid.

The symptom of otic blockage may be present for periods varying from one day to six months to even several years. In the majority of patients, symptoms are present for periods of from two days to two weeks although complaints of six to ten weeks duration are fairly common. If pain has been present, it is my experience that it takes 48-72 hours for the fluid to form after the initial pain experience. In cases of long duration, the symptoms are sometimes intermittent and the blocked feeling may disappear for short periods. Sometimes this feeling of relief may be present at various times of the day. One patient had this blockage and deafness for two years with only short intervals of relief.

I wish to re-emphasize the importance of the symptoms of deaf-

ness and blockage in the diagnosis of this infection. In many instances in which the patient complained of annoying deafness, I have not been able to discover fluid at first, even though strongly suspecting its presence. Invariably, however, after observing the drum head for a few days, I have been able to demonstrate its presence. In reiteration, if deafness seems out of proportion to the apparent pathologic change —fluid should be assiduously sought, and invariably will be found; particularly is this true if the patient can date the onset of his deafness to a definite time, say within six months.

Pain, in general, is not a marked feature of secretory otitis, and when it is present, is comparatively mild and rarely lasts more than 6-8 hours. These pain cases may represent the common acute catarrhal otitis media in an early phase, resulting in a secretory form at a later stage, possibly representing, as stated before, sequences of the same disease.

A more interesting phenomenon of otitis media with effusion is the length of time—up to many months, or even several years—that the secretion can remain in the middle ear with apparently no change. However, it is inevitable that if the secretion be allowed to remain indefinitely, the disease will go on to permanent intratympanic changes with permanent decrease in hearing acuity.

Where the mucoid secretion comes from is puzzling, as the only mucoid glands of the middle ear are present near the mouth of the eustachian tube.

Appearance of Drum Head: The appearance of the tympanic membrane is usually one of retraction; and depends on the amount of air and secretion present in the tympanic cavity at the time of examination. The fluid, if seen through a transparent tympanic membrane is tan colored or brownish pink and if the promontory is visible, a canary yellow tinge is imparted to the fluid in that area. Because of the retraction, the upper level of the contained fluid is seen as a meniscus, single if below the level of the umbo and segmented if above. If the drum head is more translucent, the fluid level is seen as a dark line, and if more opaque no fluid level may be seen at all. After seeing a sufficient number of these cases a sixth sense sometimes tells that fluid is present. In all cases comparison of the two tympanic membranes must be done and differences noted. The cases which most often are missed, are the ones in which fluid fills the entire ear cavity. Here the

change in color as compared with the other ear may help in diagnosis, or introduction of air through the eustachian tube may make the fluid more evident and on auscultation, during catheterization, the characteristic bubbling sound of air entering a fluid mass may be heard. Hotchkiss[10] and Hoople[2] have discussed very carefully the characteristic auscultation sounds heard during inflation. Many times it may be necessary to do a diagnostic aspiration to firmly establish the diagnosis.

Treatment

In all cases, it is necessary to treat the underlying nasopharyngeal condition. Any acute process in the nose, sinuses or nasopharynx should be treated with antibiotics, and the other usual methods of local therapy, including shrinkage of the mucosa of the nose, eustachian tube and careful canula suction of secretion in the nose and nasopharynx.

In order to clarify the concept of therapy in these cases with effusion, I have attempted to classify them according to their amenability to therapy.

1. *Acute Secretory Otitis Media, Mild:* a. Cases in which spontaneous resolution occurs with general treatment of the upper respiratory infection or other pathology plus hygiene of the nasopharynx.

b. Those cases that resolve following one or two inflations, by catheterization or by politzerization. These are usually secondary to upper respiratory infections, colds, acute tonsillitis and adenoiditis, mild aero-otitis, trauma, allergy. They most often present a serous secretion.

2. *Subacute Secretory Otitis Media:* a. These include the untreated or unrecognized cases.

b. Unresolved cases following inflations and simple therapy. These represent a great majority of the cases of effusion that we see. Treatment consists of aspiration or paracentesis of the tympanic cavity combined with politzerization, catheterization or suction.

I usually do an aspiration first either for therapy or if necessary for diagnosis. I use a tuberculin syringe with a #22 1¼ in. long needle. All debris and cerumen are carefully cleaned from the canal which is then painted with Tr. Merthiolate. With the patient in the sitting position, I point the needle just posteriorly to 6 o'clock on the drum head. The needle is plunged sharply through the tympanic membrane and the plunger pulled out until resistance is met showing that all fluid has been withdrawn. If one or two aspirations do not result in resolu-

tion, I then do a paracentesis of the tympanic membrane followed by inflation to drive out the contained secretion. A sweeping incision need not be made; one just slightly longer than a stab is sufficient at the usual myringotomy site. This should be followed in all cases by either spot suction at the point of incision or suction through a Siegel speculum combined with inflation of the eustachian tube through a catheter. I have found inflation perfectly satisfactory. All catheterizations should be carefully done to avoid trauma, and I usually inflate under direct visualization of the catheter movement through a nasopharyngoscope. If catheterization is inconvenient or not borne well, politizerization works almost as well. There is seldom any bleeding at the incision point, and healing occurs quickly—too quickly at times; the myringotomy wound being glued together by fibrin within 48 hours. Incidentally, it is interesting to watch the migration of the crust which forms on the drum head as a result of the aspiration. Invariably within two weeks it is seen on the canal wall.

Anesthesia is not a problem. It has been commonly noted that the uninflamed tympanic membrane can be incised without anesthesia with only slight discomfort to the patient, and many drum heads have been incised in this manner.

The results of aspiration or paracentesis and inflation are usually remarkable and even startling. The patient exclaims immediately afterwards that he hears well, and on testing the hearing, it is found to be normal or definitely improved.

The fluid from the middle ear, which collects in the canal after myringotomy—and the various methods of expelling the fluid—is removed by cotton wipes. The volume of fluid present may vary from 5-20 drops. In some cases it is clear yellow and serous in consistency—in others especially if of longer duration, it is thick and mucoid; at times so much so that it hangs like long strings. Occasionally, there may be so much fluid present that a pulsating serous discharge may be seen coming through the opening which may persist for twenty-four hours or longer. It is most likely that in these cases the fluid filled the mastoid cells as well as the middle ear.

One or two or even more catheter inflations are usually necessary for complete relief or restoration of aeration of the middle ear, although in many cases—myringotomy and one inflation are sufficient to completely relieve the symptoms. In others, several myringotomies may be neces-

sary and if the original incision is closed, which is usually the case, a new one is made without hesitancy.

3. *Recurrent Secretory Otitis Media:* a. The mild forms may recur very frequently but each recurrence is easily handled by aspiration or myringotomy followed by inflation; these may be serous or mucoid in type.

b. The moderately severe type—each recurrence of which is exceedingly difficult to control but within a reasonable time the condition is brought under control with repeated myringotomies. Some cases with recurrences are very complex. I have had many cases in which I have done up to twenty aspirations or myringotomies. Westley Hunt[11] speaks of a 69 year old physician on whom he has done eighty-three myringotomies within a six year period. This type is but a step removed from

c. The continuous and severe type which, at the risk of being accused of levity, I would term the "open spigot" or even the malignant type, in which the fluid re-forms quickly and continuously in amounts sometimes beyond comprehension. Here we have the most aggravating and puzzling form of this disease—one that taxes our every skill and patience, resisting our every therapeutic measure.

This is the form which no doubt corresponds to Jervey's[12] "Mastoiditis hyperplastica serosa" case, where the fluid is found in all the components of the middle ear—and where, in sheer desperation we do mastoidectomies, sometimes without avail. These recurrent types are where we start searching for other systemic diseases, the thyroid and other endocrine dysfunctions, the dental malocclusions, the allergies, and the autonomic imbalances that we spoke of. We have not yet found a uniform satisfactory answer to this form of the disease. If we follow the reasoning of Hilger[3]—as to the autonomic nervous system, the use of such substances as: Banthine, hexamethonium, nicotinic acid, intravenous histamine, and procaine may offer a measure of therapeutic success. This is the type in which we would like to find a good method of getting a permanent fistulous opening in the tympanic membrane, so that fluid drainage can be continuous. Some men have been using very small punch forceps. Hotchkiss[10] has adopted the ophthalmologist's corneal trephine, mounted in a long handle, using the 2 and the 2.5 mm. sizes. With this instrument he makes an opening in the posterior quadrant of the drum head, with some fairly successful results.

SUMMARY

The symptom complex of secretory otitis media, with the presence of an effusion in the tympanic cavity, has created much interest among otologists—both because an increased awareness of this condition has resulted in more frequent diagnoses, and also that there has been seemingly a marked increase in the incidence of this disease. There is a possibility that the increase of virus infections, and the attenuating effects of the antibiotics, may be factors involved in the more frequent formation of serous or mucous secretions within the middle ear. The process must be assiduously searched for in children, for here is a golden opportunity for reversing pathology before permanent changes render the processes irreversible, with permanent hearing damage.

A classification of the disease according to its amenability to therapy into acute, subacute, and recurrent types, is offered, in which consideration is given to the various modes of therapy. These range from expectant treatment in the hope of spontaneous resolution, combined with inflations, to removal of the contained secretion by aspiration or myringotomy. The troublesome aspect of some of these cases is due to the tendency in many instances for frequent recurrences to appear, sometimes so severe that we can do little to control them. It is these recurrent types, so puzzling in their nature, that make this disease so bothersome to handle. We have as yet found no uniform satisfactory answer to this form of the disease—besides trying to create a permanent fistula, a difficult and unsatisfactory procedure at best.

Treatment of local pathology that might cause chronic obstruction of the eustachian tube, is obviously an important step. The upper half lymphoid elements of Waldeyer's ring must be removed if obstructive, either by surgery, radium, or x-ray therapy. Systemic causes as endocrine disturbances or specific allergies must be investigated and treated. Hilger has offered the extremely interesting speculation that an autonomic nervous system dysfunction may cause what may be considered a vasomotor otitis media, and based on this theoretical consideration—drugs influencing the autonomic nervous system as Banthine, nicotinic acid, and intravenous histamine, and procaine—may offer a solution to this difficult problem.

Further study of secretory otitis media is necessary, for there are many unsolved aspects of this problem. It is apparent that a more

thorough understanding of the mechanism of this interesting disease, will materially aid in the solution of that old but important problem—chronic middle ear deafness.

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FOURTEENTH SERIES

POSTGRADUATE RADIO PROGRAMME

(*Continued from page 816*)

DECEMBER 1952

DECEMBER 18

7. RECENT ADVANCES IN THE MANAGEMENT OF THE DIABETIC PATIENT—Sol Sherry, *Director of the May Institute for Medical Research of the Jewish Hospital Association; Assistant Professor of Medicine, University of Cincinnati College of Medicine.*

   CANCER OF THE MAXILLARY ANTRUM—Edgar L. Frazell, *Associate Attending Surgeon, Head and Neck Department, Memorial Hospital.*

DECEMBER 25

8. RECENT CONTRIBUTIONS OF THE LABORATORY TO DIAGNOSIS AND THERAPY—Joseph C. Turner, *Associate Professor of Clinical Medicine, Columbia University; Associate Attending Surgeon, Presbyterian Hospital.*

   CANCER OF THE ESOPHAGUS—John H. Garlock, *Clinical Professor of Surgery at College of Physicians and Surgeons, Columbia University.*

The participation, criticism and counsel of the Profession in the POSTGRADUATE RADIO PROGRAMME of The New York Academy of Medicine is solicited. *Address all communications to* IAGO GALDSTON, M.D., *Executive Secretary, Committee on Medical Information,* 2 East 103 Street, New York 29, N. Y.

THE TENTH ANNIVERSARY OF THE PUBLIC HEALTH RESEARCH INSTITUTE OF THE CITY OF NEW YORK, INC.

L. WHITTINGTON GORHAM, M.D.

Director

THE tenth anniversary of The Public Health Research Institute of The City of New York was observed at The New York Academy of Medicine on April 21, 1952. The program, which follows, consisted of a morning and afternoon scientific session and a luncheon meeting.

MORNING SESSION

THOMAS M. RIVERS, M.D., Presiding
Vice-Chairman, Research Council, PHRI
Director of the Department of the Hospital
of The Rockefeller Institute for Medical Research

Antigenic Differences Among Influenza Strains

GEORGE K. HIRST, M.D., *Member and Chief, Division of Infectious Diseases*

Discussion

FRANK L. HORSFALL, JR., M.D., *Rockefeller Institute for Medical Research*

Influenza viruses may vary from one epidemic to the next in such a way that an individual who is immune to a 1943 strain of influenza A is not immune to a 1947 strain. This variation in the virus from one epidemic to the next is important in immunization studies of influenza. The present work offers evidence as to how influenza A strains may be classified as to type on the basis of the constituent antigens and this helps us to understand the basis of the variations taking place in the virus. Such an understanding is fundamental to a program of influenza prophylaxis.

Studies on Incomplete Forms of Influenza Virus

R. WALTER SCHLESINGER, M.D., *Associate Member, Division of Infectious Diseases*

Discussion

WERNER HENLE, M.D., *University of Pennsylvania School of Medicine*

When influenza virus is injected directly into the brain of mice, it mul-

tiplies but the new virus particles are not completed and they remain incapable of infecting other hosts. Biological and electron microscopic properties of the incomplete virus particles were described.

The Role of Adjuvants in Immunization and Sensitization

JULES FREUND, M.D., *Member and Chief, Division of Applied Immunology*

Discussion

JONAS E. SALK, M.D., *University of Pittsburgh School of Medicine*

The incorporation of vaccines in a small amount of paraffin oil enhances and sustains immunity. This type of vaccine is being tested in man elsewhere. The addition of killed tubercle bacilli or saprophytic acid-fast bacilli to paraffin oil further augments antibody formation and promotes sensitization to antigens. The use of "adjuvants" is a useful tool in experimental medicine.

Adrenal Hormones in Murine Tuberculosis

HUBERT BLOCH, M.D., *Member, Division of Applied Immunology*

Discussion

WALSH MCDERMOTT, M.D., *Cornell University Medical College*

Cortisone has been shown to enhance considerably the course of tuberculous infections, both in man and animals. This action being of practical as well as theoretical importance, experiments were designed to clarify the mechanism of this effect. It could be shown that, if cortisone is given along with certain other adrenal hormones, its enhancing action is neutralized. The effect observed is, therefore, not a direct action of cortisone but rather due to interference of cortisone with the normal equilibrium between the hormones of the adrenals and other endocrine organs. Experiments have shown that adrenal hormones play an important part in natural resistance to tuberculosis, the significance of which is only just being recognized.

AFTERNOON SESSION

VINCENT DU VIGNEAUD, Ph.D., Presiding
Professor of Biochemistry,
Cornell University Medical College

Metabolic Relationships of Proline, Hydroxyproline and Ornithine

MARJORIE R. STETTEN, Ph.D., *Associate, Division of Nutrition and Physiology*

The metabolic interrelationships of certain amino acids have been studied, using isotopically-labeled compounds fed to rats. Proline is converted in vivo into hydroxyproline, glutamic acid and ornithine. In the demonstrated conversion of ornithine into proline and glutamic acid, it is the δ rather than the α-amino group of ornithine which is retained. Glutamic acid semialdehyde is a likely intermediate in all of these interconversions. In contrast to all other amino acids studied, hydroxyproline, when

fed, is not well utilized in protein synthesis. Such hydroxyproline as occurs is derived from proline already bound.

Biological Interconversions of Hexoses

YALE J. TOPPER, Ph.D., *Associate, Division of Nutrition and Physiology*
MURRAY M. LIPTON, Ph.D., *Associate, Division of Applied Immunology*

The biosynthesis of capsular polysaccharide, principally hyaluronic acid, by group A hemolytic streptococci was discussed. This polysaccharide, which is composed of equal numbers of N-acetyl glucosamine and glucuronic acid residues, is very similar to the hyaluronic acid which has been isolated from vitreous humor and umbilical cord. By the use of radioactive glucose, the mechanism by which the microorganism makes the constituent sugars of the capsular material has been studied.

Also, the mechanism by which the rat converts galactose, a component of milk sugar, immunological polysaccharides, brain lipids, etc., into glucose was described.

Studies in Experimental Diabetes

DEWITT STETTEN, JR., M.D., Ph.D., *Member and Chief, Division of Nutrition and Physiology*

The results of a collaborative study with Dr. Dwight J. Ingle of the Upjohn Company, Kalamazoo, have been described. By a combination of continuous intravenous injections and isotope dilution techniques, the rate of glucose synthesis in the intact rat has been measured. This rate has been found to be somewhat increased in alloxan-diabetic rats, and greatly increased, up to seven times normal, in rats receiving cortisone. Whereas marked impairment of glucose oxidation occurs in diabetes, no such interference was observed in cortisone-treated animals.

The Molecular Configuration of Glycogen with Remarks about Glycogen Storage Disease

CARL F. CORI, M.D., *Washington University School of Medicine*

Analysis of the products obtained when glycogen is alternately digested by phosphorylase and by amylo-1, 6-glucosidase, make possible a determination of the details of structure of the polysaccharide. Glycogen was shown to have a multi-branched, tree-like structure, with a single reducing end and five or more tiers of branch-points. The average number of glucose residues which are situated at the branch-points is approximately 6-8 per cent of all of the glucose residues in the molecule.

The livers from ten patients with von Gierke's disease have been studied. In two of these which were fatal at an early age, a deficiency of the enzyme glucose-6-phosphatase was encountered. In two others, no enzymic defect was evident but the structure of the liver glycogen was found to deviate markedly from that observed in glycogen from normal livers. In one of these, the glycogen resembled the amylopectin component of vegetable starch.

History of the Institute

At the luncheon meeting, the historical background and development of the Institute were presented by Dr. Michael Heidelberger, Chairman of the Research Council, and by Mr. David M. Heyman, Chairman of the Board of Directors. The guest speaker at noonday was the Surgeon General of the United States Public Health Service, Dr. Leonard A. Scheele. His address, entitled "Public Health Research," is published in this issue of the Bulletin.

The story of the organization, administration, growth and scientific contributions of The Public Health Research Institute is indeed a fascinating one. To understand the significance of this, its tenth anniversary, one must examine the rich heritage of New York City in the field of Public Health, which dates back nearly half a century. In 1893, Dr. Hermann M. Biggs, Commissioner of Health, and Dr. William Hallock Park, Director of the Bureau of Laboratories, won world-wide recognition for New York City's Health Department by their work in diphtheria. For approximately forty years, a series of important contributions was made by the City Health Department and the Bureau of Laboratories. These included the reduction of diphtheria deaths from about 3,000 annually to almost the vanishing point; the general pasteurization of milk, which virtually eliminated the bovine tubercle bacillus as a cause of morbidity among the City's children, and a great diminution in milk-borne epidemics of streptococcal diseases. Also, the discovery of new types of pneumococci by Georgia Cooper and Annabel Walter greatly increased the knowledge of this important group of organisms and pointed the way to the extension of therapy by type-specific antisera produced in the rabbit that offered the only hope of cure of pneumonia until the introduction of the sulfa drugs. Meanwhile, the Convalescent Serum Laboratory, under Dr. William Thalhimer, was steadily increasing its distribution of sera for the modification of measles and scarlet fever, and was winning recognition from medical practitioners all over the Greater City. Under way at this time, also, was the first large-scale testing of BCG vaccination under Park, Mishulow and associates.

In 1936, the needs of an expanding research program led to the formation of a non-profit organization, Health Research, Inc., by a group of workers from research institutions and medical schools. In

1941, this became The Public Health Research Institute of The City of New York, Inc. A contract was made with this body by which the City agreed to pay the Institute the sum of $100,000 annually to support research and investigation related to the various problems of Public Health for the benefit of the people of the City of New York. In addition, the City agreed to provide suitable laboratory space and maintenance. The annual compensation has been increased by steps until it now amounts to $400,000 with fourteen years of the contract still to run.

The Institute, as far as is known, is unique among municipal laboratories; the method of financing it may appear unusual at first glance but it is quite similar to that employed to support other non-profit organizations, such as the American Museum of Natural History, the Metropolitan Museum of Art, and the New York Public Library. Like these institutions, it may and has received substantial financial aid from outside sources while, at the same time, it assures the City of unrestricted research in Public Health at a very high level.

The enviable and outstanding position which the Institute has attained in the scientific world in a period of ten years is not recognized by the general public. Its successful operation during this period has naturally depended upon several factors; primarily, of course, upon the unusually high caliber of its scientific staff and the quality of the work they have produced. Credit for the foundation and organizational pattern of the Institute is rightfully shared by far-sighted City Administrations and by a small group of interested scientists and laymen.

The Institute operates under an eleven-member Board of Directors on which the City is represented by the Mayor, the Comptroller, the Commissioner of Health and the Commissioner of Hospitals. The other members are chosen for their experience and skill in administrative affairs.

The Research Council, which is composed of a group of nine scientists of recognized ability in various fields, administers the scientific affairs of the Institute through a Director assisted by a Business Manager.

The Institute shares a building with the Bureau of Laboratories at the Foot of East 15th Street, adjoining the Willard Parker Hospital at the East River. These quarters are inadequate to meet the demands of an expanding City health program, which are being made both on the Bureau of Laboratories in the diagnostic division and upon the Institute in research. The satisfactory solution of this problem is of supreme

importance for the future and serious thought is being given to it.

The notable contributions of the Institute during the past ten years include the cooperation with the City Health Department in planning and carrying out the first large-scale gratis vaccination of dogs against rabies in Richmond in 1947 – work which is still going on; the development of a slow absorbing type of penicillin; the early preparation of a triple vaccine against whooping cough, diphtheria and tetanus, combining in one dose all three of these antigens; the establishment of an Rh Laboratory in collaboration with the Bureau of Laboratories; the establishment of a Virus Diagnostic Laboratory for the City; emergency diagnosis of smallpox by isolation of virus in threatened epidemic of 1947 and, in 1950-1951, the isolation of a new substance from tubercle bacilli known as the "cord factor," which plays a conspicuous part in its virulence.

At the present time, important investigations are in progress dealing with the use of adjuvants which make possible the great enhancement of the immunity obtainable by injecting vaccines; also, studies on intermediary metabolism with the labeled isotope technique, which will broaden our knowledge of nutrition. Likewise, fundamental studies of much importance in the field of viral diseases are under way, including the more accurate diagnosis and classification of various types of epidemic influenza, the problem of effective immunization, the studies on dengue fever, virus encephalitis and mouse poliomyelitis. Finally, at the Goldwater Memorial Hospital, the Institute is supporting investigations in the Research Divisions of Columbia University and New York University dealing with arteriosclerosis and the problems of the aged.

PUBLIC HEALTH RESEARCH*

LEONARD A. SCHEELE

Surgeon General, Public Health Service, Federal Security Agency

I FEEL it a special privilege to participate in the tenth anniversary of the Public Health Research Institute of the City of New York. This Institute and the Public Health Service share, with more than usual intimacy, a glorious heritage. To this day, that close relationship has been preserved. Then, too, it is a privilege to be here because relatively few research institutes in our country have grown out of a public health agency and remained the scientific arm of a state or city government. As tax-supported institutions integrated with broad public health and hospital programs, the Public Health Research Institute of New York City and the National Institutes of Health of the Public Health Service are not unique—but they have very few counterparts sharing a common background, common problems and objectives.

It is pleasant to recall that research in the Public Health Service began here in New York City less than a decade before William H. Park launched the same adventure in the City Health Department. As Dr. Park's laboratory was the cradle of the Public Health Research Institute, so also Dr. Joseph J. Kinyoun's Hygienic Laboratory in the Marine Hospital on Staten Island was the cradle of our National Institutes of Health.

Dr. Park focussed his brilliant mind first upon diphtheria. When he came to the New York City Health Department in 1893, the diphtheria death rate hovered around 100 per 100,000 population. In 1887, Dr. Kinyoun undertook to determine whether the cholera vibrio would survive in New York Bay. Cholera had entered the United States through New York in 1832. Again it struck in 1854, 1866, 1867, and 1873. The introduction of cholera by merchant seamen and immigrants arriving at the Port of New York was a problem of first importance to the Nation—and hence to the Public Health Service.

As we try to probe the mists of time that veil those bygone years,

* Delivered at the Tenth Anniversary of the Public Health Research Institute of the City of New York, Inc., New York, N. Y., at The New York Academy of Medicine, April 21, 1952.

we would like to recapture some of the enthusiasm that spurred those two pioneers. To them, the conquest of diphtheria and cholera seemed as far a frontier as the conquest of cancer seems today. Yet within the lifetimes of Park and Kinyoun, public health agencies and private physicians were given the means to prevent both diphtheria and cholera. These and many other epidemic diseases had capitulated or were beating a rapid retreat.

In Dr. Kinyoun's first annual report on the Hygienic Laboratory, he wrote "the scope of work of this character is constantly widening, its utility unquestionable."[1] History has verified that prediction. The vital records of this city and of the Nation are proofs positive that public health research—ever extending its scope—has produced a vast amount of useful knowledge for the improvement of human health.

Those of us who are public servants can be proud that governmental laboratories have borne an honorable share of this scientific effort—along with the universities, medical schools, private foundations, and industrial laboratories. As the Public Health Research Institute honors the names of Park and Biggs for their attack on diphtheria, so the Public Health Service honors Stiles for his fight against hookworm; Ricketts, Parker, Spencer, Dyer, Cox, and others against the rickettsial diseases; Goldberger and his co-workers against pellagra. The New York State Laboratory also calls to mind the contributions of Wadsworth and others to the serology of syphilis.

The names I have mentioned make up only a fraction of the entire list of governmental scientists, living and dead, whose work is already enshrined in the legends of public health. In these public health laboratories today, hundreds of others are conducting investigations that challenge the best thought and they are constantly enriching our understanding of public health problems.

Dr. Gorham said that I might include in my discussion some remarks on why research is important in public health. The history of the Public Health Research Institute and of the National Institutes of Health provides the best answer to that question. Let us pursue the point a little farther.

Progress in public health, like advances in all other fields of human endeavor, springs from the results of scientific research. We need only to turn to the father of scientific method for a clear expression of the aims and results of research. In *Novum Organum*, Bacon states it thus:

"Man, being the servant and interpreter of nature, can do and understand so much and only so much as he has observed in fact or in thought of the course of nature: beyond this he neither knows anything nor can do anything. . . . Human knowledge and human power meet in one; for where the cause is unknown the effect cannot be produced."

In our Western civilization, this very linking of science and action is the force which has made—is making—human life easier, safer, and healthier. We see its fruits in the increasing productivity of our own Nation, the amazing volume and variety of goods and services, the release from long hours of arduous labor, and our longer average life expectancy.

Science and its application have flourished in our democratic society throughout the lifetime of our Nation. And this freedom of thought and action is due in no small part to the eager vision of our founding fathers. Their concept of government as the guardian of peace, security, and liberty, recognized that the discharge of this responsibility would require government to be a partner of the people in many adventures of the human spirit.

"Laws and institutions," wrote Thomas Jefferson, "must go hand in hand with the progress of the human mind. As that becomes more developed, more enlightened, as new discoveries are made, new truths disclosed, and manners and opinions change with the change of circumstances, institutions must advance also, and keep pace with the times."[2]

Jefferson did more than any other of our early presidents to integrate scientific effort with the government's contribution to the general welfare. Bernard de Voto gives us a vivid picture of one of the earliest scientific adventures of the Federal Government in his description of the Lewis and Clark Expedition.[3]

"They toiled westward . . . fulfilling a dream which Meriwether Lewis had had in his boyhood, fulfilling an older, more complex dream of Jefferson's, and by strength and skill and valor they rolled the unknown back before them. The country ahead of them was an untraveled chaos, the boundary of men's knowledge moved with them, they passed and the map was made forever."

The opening of the frontier presents many analogies with public health research. For the individual scientist, the boundary of man's knowledge is the eternal challenge; moving it forward, his undying dream. For the society which benefits by the scientist's efforts, it is

the new knowledge, the new line on the map that challenges to application. For the government that participates in or supports research, it is the responsibility to secure the blessings of liberty—both to society and to science.

The fuse that drives public health research, then, is identical with that which motivates all scientific endeavor: namely, curiosity about nature. We must recognize in public health research, however, a second motivation of equal force. This is the desire of man to secure for himself and posterity a better life. As a result, public health research must take account of the specific aims of the society in which it functions.

I hasten to say that this yearning of the people for better health, for improvement in particular areas such as chronic disease, does not result in control of science. The organization and administration of the Public Health Research Institute of New York City is proof of that statement. I am proud to say that the same is true of the Public Health Service's research program.

The scientists in our laboratories and those who receive financial support from us in outside institutions are assured complete freedom in the planning and conduct of their investigations. Moreover, the relationship of our appropriating bodies to our institutions is in the best tradition of constitutional governments. Once the Public Health Service goes before the Congress, or your Board of Directors goes to the City Administration, and funds are made available, there is complete freedom for use of research funds.

In contrast, consider the "thought control" under communism which has debased Russian science in recent years. The pursuit of truth cannot flourish when men are required to conform their thoughts to the ideology of a political party on the one hand, and to a specified scientific tradition on the other.

In a free environment, such as our democracy assures, the findings of a Lysenko are validated by the scientist's peers, freely subjecting his hypotheses and conclusions to the acid test of further search for truths. So long as freedom exists anywhere in this world, the human mind will continue to resist the imposition of "truth" by fiat.

As we read today of Russian scientists confessing to the "crime against the people" of seeking truth and enunciating it,[4] we realize anew and with a singular dread that tyranny of the spirit is also tyranny of the body, no matter how allegedly humanitarian may be the terms in

which it is imposed. There is high tragedy, too, in the arbitrary deification of a scientific tradition such as the Soviet's official policy of permitting only the application of Pavlov's principles in basic and applied psychological research.

One wonders what would be the fate of Pavlov himself today: Pavlov who wrote at the age of 87, the following advice to the youth of Russia devoted to science:

"Never attempt to screen an insufficiency of knowledge even by the most audacious surmise and hypothesis. Howsoever, this soap bubble will rejoice your eyes by its play, it inevitably will burst and you will have nothing but shame. . . . Learn, compare, collect the facts! But learning, experimenting, observing, try not to stay on the surface of facts. Try to penetrate to the secret of their occurrence, persistently search for the laws that govern them."[5]

Scientists and institutions who depend largely for financial support on outside fund-granting agencies often face a difficult problem in maintaining continuity of their investigations. Among governmental institutions, the contract plan of the Public Health Research Institute is unique, I believe. Your City Government has shown remarkable foresight and courage, not only in founding such an Institute, but also in developing a system which assures continuity of appropriations over a 17-year period and on a rising scale. Your staffs and your grantees are thus given a valuable sense of security.

Under a different system of financing, the Public Health Service has maintained a complete continuity in its research grants programs through the foresight of Congress. In our research grants program, more than one fourth of the projects first aided in 1946 received fifth renewals in 1950.

Perhaps in no scientific field is it more difficult to draw a distinction between fundamental research and applied research than in the study of man. In recent years, I have heard a great many discussions by distinguished scientists and research directors on what kinds of research should be encouraged or emphasized. The literature on the subject is growing.

As one follows the discussion, one becomes aware of sharp cleavages of opinion. New terminology has been suggested. For "fundamental," or "basic," or "pure" research, it is now proposed that we speak of "unrestricted" or "uncommitted" research. What has been

termed applied research and development, we are now asked to call "committed," or "objective," or "programmatic" research.

To distinguish fundamental and applied research, James B. Conant in his capacity as Chairman of the National Science Board, has used a figure of speech which appeals to me strongly. "Applied research," he says, "is like drilling for oil when you know where the oil is. Fundamental research is like prospecting for oil in a hitherto unexplored country."[6]

This analogy clearly discriminates the nature of the scientific problems which challenge human thought. Most scientists and research directors are aware that, by and large, the prospecting for pay dirt—fundamental research—must precede the drilling. They are also aware that scientific effort in this country until recent times has generally emphasized the drilling—in new territory prospected first by pioneers in Europe. Since World War II, strong efforts have been made to correct that imbalance. A major objective of the Public Health Service's research programs, for example, is to promote basic research in the health and medical sciences. The rapid increase of private and public support of public health research in recent years demonstrates the concern of the American people for scientific advances in this field.

It seems to me, however, that by classing scientific research as "unrestricted" or "uncommitted," on the one hand, and as "programmatic" or "objective," on the other, we are perhaps confusing the organization and administration of research institutions with the nature and quality of scientific effort. In my opinion, all types of scientific investigation—fundamental, applied, clinical, epidemiologic, social, developmental, call them what you will—should be encouraged in all qualified institutions.

In the thinking of many distinguished scientists and administrators, the planning of large-scale research programs to be carried on by organized groups offers a serious threat to the freedom of the individual investigator. They fear that if too many competent workers are involved in planned programs, the opportunities for basic scientists to follow their hunches will be diminished. Hence, the great syntheses of thought which are the points of departure for striking new advances in science will occur less frequently.

It is a mistake to assume that the pressure for large-scale research on specific health problems will inevitably result in such a drying up of the springs of knowledge. Science, like every other field of human

thought, will always await the individual whose genius makes possible the forward leap in the dark. We know that the scientific environment of by-gone centuries—particularly of the Nineteenth Century—is not the only environment which can foster genius. If those of us who administer research programs or who sit on Boards and Councils of research organizations are worth our salt, we will strive to assure maximal opportunity for basic research freedom.

Research today is of a different order than in earlier times and the changes have sprung from scientific progress itself. In public health and medical research, for example, there is a significant movement today toward the exploration of the underlying physical, chemical, and electrical characteristics of protoplasm and of biological systems. The most brilliant investigator, however, cannot solve his problem without the tremendous resources of modern instrumentation and techniques of measurement; without highly skilled assistants; and without close contact with his colleagues in a variety of disciplines. The fact that funds, organization, and administration are required to provide him with the essential facilities, staff, and scientific collaboration need not—should not—diminish in any degree his intellectual freedom. In fact, they should enhance it.

Experience has shown that a concerted planned attack on some problems may produce valid results in a shorter time than could be expected without such planning. This does not mean, however, that all of our major public health problems will yield to such an attack.

We are aware that chronic diseases and understanding of the processes of aging are the chief unsolved problems in public health research today. The very nature of these problems requires a high degree of flexibility and variety in research institutions. Despite the recent increases in governmental, voluntary, and industrial support of research in the health sciences, we are still barely scratching the surface in such unexplored territories as cancer and the cardiovascular, metabolic, and neurological diseases, and rehabilitation. Augmented support of research in these and other fields is needed—from all sources.

Public health research programs especially should be concerned with this need. This Institute has already demonstrated how a research program, integrated with a public health agency, can advance science and at the same time can advance the public health and hospital services of a great city. Your Diagnostic Rh Laboratory and Diagnostic Virus

Laboratory are good evidence of the inter-relationship of fundamental research and public health practice.

Now and in the future, state and local health departments, hospitals, and welfare agencies depend on progress in health and medical research for methods to control chronic disease and to promote better health and vigor in the aged. As our population grows and ages our medical, social, and economic resources will carry an increasing and all but insupportable burden so long as we lack the fundamental and practical knowledge of the causes, prevention, cure and rehabilitation of chronic disease and disability.

The people of the United States realize this need to a remarkable degree. It is because of their understanding of the importance of science to national welfare that they have increased public support of research through voluntary subscription of funds or through governmental appropriations. The problems which attract their attention in public health research are human problems which all of us face every day. Happy, vigorous old age and freedom from pain and premature death are natural aspirations of the human race. Hence, these are also the goals of public health. In this sense, public health research will always be "objective."

The American people have a touching faith that scientists and research institutions can find the way to reach those goals. One of the most refreshing aspects of our Public Health Service research program, for example, is that neither the Congress nor the Executive Branch of Government, neither the public nor the professions have tried to tell us or the scientists whose work is supported by our grants how to go about getting the answers. Thus, in our research programs on cancer, heart disease, arthritis, nervous and mental disease, you will find investigations in the basic sciences leading to conclusions remote from the specific problem. You will also find highly organized teams, committed to a particular accomplishment, whose members perform according to specified standards under close supervision. In either case, full authority for the design of the study, the quality of the research, and the results is left in the hands of the responsible scientists.

A great citizen of New York, Judge Learned Hand, whose passion for freedom is a part of our Nation's spiritual heritage, has expressed the glory of man's individuality and his insistence on "meddling." "Without the meddling," he wrote, "nothing would have happened of all that glo-

rious array of achievements. . . . My thesis is that any organization of society which depresses free and spontaneous meddling is on the decline, however showy its immediate spoils."

Public health research in our country has flourished in an environment of free and spontaneous meddling. The benefits to our society and to the world have been immeasurable. I am sure that we can predict greater benefits as our research programs extend their scope and intensity. The governmental research laboratory and the privately supported laboratory pursue the same ultimate goals under the same dispensations of freedom.

In the future, I hope that more of our state and local governments will establish research programs integrated with their health and hospital services and that these will work intimately with our universities and voluntary institutions. Among our great metropolitan centers, New York City has led the way. The achievements of the Public Health Research Institute have shown that tax-funds can be profitably invested in fundamental research. The value to public health agencies is in the stimulation of scientific study and the impact of new ideas. For as Pasteur wrote, "without theory, practice is but routine born of habit."

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NEW YORK PATHOLOGICAL SOCIETY

Abstracts of Papers

Presented at the Meeting, April 24, 1952 at The New York Academy of Medicine

The Incidence of Cystic Disease In So-Called "Normal" Breasts

A STUDY BASED ON 225 POST-MORTEM EXAMINATIONS

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This study was undertaken in the hope that it might establish a figure for the incidence of cystic disease of the breast in the population as a whole, and further document previous studies reported from the Presbyterian Hospital in New York and from other clinics concerning the relationship of so-called "chronic cystic mastitis" to carcinoma. It is to be followed by a similar analysis of an equal number of surgical specimens of cancerous breasts. Dr. Stout has already presented figures from this hospital showing a significantly higher incidence of cystic disease in cancerous breasts than in this autopsy series, but the author and her collaborators hope to analyze the gross and microscopic findings in cancerous breasts in somewhat more detail in a comparable series studied from the start with their criteria in mind. These two comparable series *might* throw some light, for instance, on the significance of epithelial hyperplasia. It has often been suggested, particularly by clinicians, that simple cystic disease may not be associated with carcinoma but that cystic disease with certain types of epithelial proliferation may well be a pre-cancerous lesion. This has sometimes led to bilateral mastectomy as a prophylactic measure.

Similar autopsy series have been published from other laboratories, and the largest previously reported, as far as we have been able to determine, consists of 100 autopsy subjects. Our findings in 225 subjects confirm most of the earlier work. Other approaches to the problem are, of course, through examination of surgical material, and long follow-up observation of patients who have undergone operation previously for benign lesions of the breast. If such patients develop carcinoma in a higher proportion than the expected incidence in the population as a whole this would be further evidence of the relationship of cystic disease to cancer. It would not, however, establish the relationship as a causal one. Such studies are also in progress in our laboratory and follow-up clinic.

In the extended article which has already appeared in *Cancer* (with co-authors Pickren, Melcher and Auchincloss) these considerations are discussed at more length and the histological findings in our series, presented in lantern slides to the New York Pathological Society, are shown in this article in twenty-six photomicrographs. These form the basis for the statistics in the fifteen tables which also appear in *Cancer*, some of which are reproduced here.

Gross cystic disease, as will be seen in the tables, occurred in 18 per cent of the cases.

Any case showing even a single 1 to 2 mm. blue-domed cyst was so classified. If microcysts and apocrine epithelium as the only findings are considered to constitute disease this "microcystic" variety raised the incidence to 53 per cent of all cases. These two findings, constituting minimal disease, were the only findings in 24 per cent of the cases. If this minimal "disease" is excluded, cystic disease with epithelial proliferation, usually slight, and always bilateral, was found in 28 per cent of the cases. It is this figure, 28 per cent, which the author is anxious to correlate with the findings in the cancerous breasts being studied now. In only six of forty-two cases of gross cystic disease in this autopsy series—disease revealed by the pathologist's serial sections—would a surgeon, exploring the breast, have had reason to consider it abnormal, and in only one case was there a cyst large enough to have been palpated on physical examination. This happened to be on the deep aspect of the breast so it might well have been missed. Routine physical examination of these 225 women before death would, therefore, have given no hint of the pathological findings, unless irregularities, palpable during life, bilaterally, are interpreted as disease by the breast conscious physical examiner. This is a fairly frequent misinterpretation in the author's opinion.

Markedly dilated nipple ducts in the older age group and a low incidence of proliferative epithelial disease after surgical sterilization were additional findings of interest. In conclusion it may be said that there was an exceedingly low incidence of cystic disease as the surgical pathologist finds it in surgical specimens of breast tissue removed for benign lesions. There was also a lower incidence of cystic disease—probably statistically significant—than is found in breasts removed for cancer.

DISCUSSION

Arthur Purdy Stout: This study by Dr. Frantz and her associates represents an important contribution to our body of knowledge. It establishes that in an autopsy population of 225 women without known breast disease, some evidence of proliferative activity was present in 53 per cent, or 118 cases. In addition, there were twenty-one women with fibroadenomas, four of whom had no cystic disease. There were no gross intraductal papillomas. One could say therefore supposing fibroadenomas to be evidence of proliferative activity, past or present, that the 118 cases might be increased to 122 or 54.2 per cent, hardly a significant advance. This figure compares with the 74 to 79 per cent of cystic disease found in cancerous breasts and, of course, raises the perennial question of the relationship of cystic disease to cancer of the breast.

Before discussing this question I should like to say that for many years I have been confused by the multiplicity of names attached to fibroadenomatosis or cystic disease and the various kinds of benign breast tumors composed of stroma and glands including all the varieties of fibroadenomas and gross and microscopic papillomas. It has been a mistake, I believe, to talk of these lesions as if each one was a separate entity without relationship with the others or with cystic disease. It is my opinion that all of them are probably hormonally induced even if they appear for the first time after the menopause, and that all of them are of the nature of hyperplasias of breast elements manifesting themselves under the various guises to which these different names have been applied. Thus it does not surprise me that Dr. Frantz has been able to identify all of them in the group of autopsy breasts except gross intraductal papilloma. I assume this is absent for in most cases this lesion is associated with a discharge from the nipple, a sign sufficiently discommoding to lead most women to have the offending growth removed. I find it convenient to group all of these lesions under the common label fibroadenomatosis, a name which was used by Semb for all the varieties of cystic disease, but which may very conveniently be stretched to include the various so-called fibroadenomatous proliferations as well.

Supposing, then, that all these evidences of proliferative activity may be grouped together, it is pertinent to ask does the discrepancy between 74 to 79 per cent of

TABLE 1—FINDINGS IN 225 CASES ACCORDING TO AGE GROUPS*

Finding	All		Age, yrs. 0-19		20-29		30-39		40-49		50-59		60-69		70-79		80-89	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at death	225	100	7	3.1	14	6.2	30	13.3	43	19.1	57	25.3	44	19.6	21	9.3	9	6.3
Gross cystic dis.	42	18.6	0	0.0	3	21.4	6	20.0	15	34.9	9	15.8	4	9.1	3	14.3	2	22.2
Gross and micro. prolif. cystic and/or apocrine epithel.	118	52.5	0	0.0	4	28.6	18	60.0	23	53.5	30	52.6	22	50.0	15	71.4	6	66.7
Gross and micro. (prolif.) dis.	63	28.0	0	0.0	4	28.6	10	33.3	17	39.5	13	22.8	9	20.5	7	33.3	3	33.3
Microcystic dis. with apocrine cells only	55	24.4	0	0.0	0	0.0	8	26.7	6	14.0	17	29.8	13	29.5	8	38.1	3	33.3
Microcystic dis. with simple microcysts only	33	14.7	1	14.3	3	21.4	5	16.7	9	21.0	6	10.5	4	9.1	4	19.0	1	11.1
Dilated ducts	54	24.0	0	0.0	1	7.1	2	6.7	6	13.9	10	17.5	21	47.7	11	52.4	3	33.3
Inverted nipples	13	5.8	1	14.3	0	0.0	1	3.3	0	0.0	3	5.3	4	9.1	2	9.5	2	22.2
Secretory cells	7	3.1	0	0.0	0	0.0	1	3.3	4	9.3	1	1.8	0	0.0	1	4.8	0	0.0

TABLE 2—ANALYSIS OF GROSS CYSTIC DISEASE

Finding	All		Age, yrs. 0-19		20-29		30-39		40-49		50-59		60-69		70-79		80-89	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total cases	42	—	0	—	3	—	6	—	15	—	9	—	4	—	3	—	2	—
Intraduct. prolif.	19	45.2	0	0.0	1	33.3	1	16.7	7	46.7	4	44.4	3	75.0	1	33.3	2	100
Adenosis	7	16.7	0	0.0	0	0.0	1	16.7	2	13.3	3	33.3	1	25.0	0	0.0	0	0.0
Apocrine epithel.	34	81.0	0	0.0	3	100	3	50.0	13	86.7	7	77.8	4	100	2	66.7	2	100
Dilated ducts	11	26.2	0	0.0	0	0.0	0	0.0	2	13.3	4	44.4	2	50.0	2	66.7	1	50.0
Foam cells	25	59.5	0	0.0	3	100	3	50.0	10	66.7	4	44.4	2	50.0	2	66.7	1	50.0
Lymphocytes	12	28.6	0	0.0	0	0.0	4	66.7	4	26.7	3	33.3	0	0.0	1	33.3	0	0.0
Inverted nipple	2	4.8	0	0.0	0	0.0	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0	1	50.0
Fibroadenoma	4	9.5	0	0.0	0	0.0	0	0.0	2	13.3	2	22.2	0	0.0	0	0.0	0	0.0
Gross	1	2.4	0	0.0	0	0.0	0	0.0	1	6.7	0	0.0	0	0.0	0	0.0	0	0.0
Micro.	3	7.1	0	0.0	0	0.0	0	0.0	1	6.7	2	22.2	0	0.0	0	0.0	0	0.0
Known postmenopausal	20	47.5	0	0.0	0	0.0	1	16.7	3	20.0	7	77.8	4	100	3	100	2	100
Ovarian follicles not found	27	64.4	0	0.0	0	0.0	2	33.3	9	60.0	7	77.8	4	100	3	100	2	100

* All these tables are reprinted from an article by Frantz, V. K. et al, in *Cancer 4:762-83, 1951*, with the permission of the publisher.

TABLE 3—FINDINGS ASSOCIATED WITH MARKEDLY DILATED NIPPLE DUCTS ("ECTASIA")

Finding	All		Age, yrs.													
			0-19		20-29		30-39		40-49		50-59		60-69		70-79		80-89	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total cases	54	—	0	—	1	—	2	—	6	—	11	—	21	—	10	—	3	—
Postmenopausal	52	96.3	0	0.0	0	0.0	1	50	6	100	11	100	21	100	10	100	3	100
Gross cystic dis.	11	20.4	0	0.0	0	0.0	0	0.0	2	33.3	4	36.4	2	9.5	2	20.0	1	33.3
Gross and micro. (prolif.) dis. and/or apocrine epithel.	27	50.0	0	0.0	0	0.0	1	50.0	2	33.3	3	27.3	11	52.3	8	80.0	2	66.7
Microcystic dis. with apocrine cells only	3	5.6	0	0.0	0	0.0	1	50.0	1	16.7	0	0.0	1	4.8	0	0.0	0	0.0
Foam cells	19	35.2	0	0.0	1	100	1	50.0	2	33.3	3	27.3	7	33.3	4	40.0	1	33.3
Lymphocytes	19	35.2	0	0.0	1	100	1	50.0	1	16.7	4	36.4	8	38.1	2	20.0	2	66.7
Inverted nipples	6	11.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	3	14.3	2	20.0	1	33.3

TABLE 7—SIGNIFICANCE OF ADENOSIS AND APOCRINE CELLS

Finding	Total cases	Cases with adenosis		Cases with apocrine cells	
		No.	%	No.	%
Total cases	225	14	6.2	107	50.7
Gross cystic dis.	42	7	16.7	34	80.9
Intraduct. papillary prolif.	21	5	23.8	20	95.2
Intraduct. solid prolif.	30	2	6.7	25	83.3
Fibroadenoma	21	1	4.8	—	—
Microcysts only	55	—	—	55	100

TABLE 14—SIGNIFICANCE OF BILATERAL OOPHORECTOMY

Postop. interval, yrs.	Age at death, yrs.	Gross cystic dis.	Micro-cystic (prolif.) dis.	Micro-cystic dis. with apocrine cells	Micro-cysts only
1	57	0	+	+	0
1	49	0	0	+	0
3	38	0	+	0	0
3	83	0	0	+	0
8	67	0	0	0	0
12	42	0	0	0	0
14	51	0	0	0	0
15	51	0	0	0	0
15	60	0	0	0	0
27	45	0	0	0	0
28	54	0	0	0	0
36	73	0	+	+	0
46	73	0	0	0	+
?	64	0	0	0	0
?	66	0	0	0	0
?	71	+	+	+	0
16 cases	16 cases	1 6.3%	4 25%	5 31.3%	1 6.3%

TABLE 15—COMPARATIVE SERIES

Author	No. of cases	Cystic disease, %
Breast Cancer		
Stout	410	79
Foote & Stewart	300	74
"Normal Breasts"		
Semb	32	3
Lindgren	60 (120 breasts)	32 (breasts)*
Franzas	200	55
Frantz et al.	225	53

* Might be assumed to be bilateral disease.

—Reproduced from CANCER, Vol. 4 (4):762, July, 1951

fibroadenomatosis found in breasts containing cancer, while only some 54 per cent of autopsy breasts show some evidence of this process, mean that cancer is more prone to develop in the breast showing fibroadenomatosis? I have found this a question impossible for me to answer. First, because there is no general agreement among statisticians as to the actual cancer development rate in the female population at various age levels; second, because in order to prove that a woman has cystic disease, part of her breast tissue must be removed which may mean that the area of greatest proliferative activity may have been removed; third, because in order to learn of the cancer development rate in women proved to have fibroadenomatosis a considerable group of them must be followed for the rest of their lives, which can easily mean thirty to forty years, and finally, because of the impossibility of proving that a given cancer developed from epithelial cells in an area of fibroadenomatosis. One would suppose that the best chance to do this would be in intraductal papillary growths, whether gross or microscopic. I have studied many sections with this in mind and have never been able to convince myself that I could find a transformation of the epithelial cells of a benign intraductal tumor to cancer cells. I suppose it must occur occasionally, for there is no reason to suppose this proliferated epithelium is any less likely to become cancerous than any other duct cells, but while I have seen intraductal and intracystic papillary carcinomas of the breast, they were altogether cancerous and not part benign and part cancerous. I once saw what seemed to be such a transformation in a papillary sweat gland tumor, but never in the breast. It will not prove anything to say that one can find hyperplastic and cancerous cells juxtaposed in a duct, for it is well known that cancer can spread within a duct from one part of the breast to another, and in a fixed and stained preparation it is not possible to tell what biological activity preceded the moment of removal and fixation.

Dr. Frantz and her associates have provided us with an important basic observation which is essential to the story of cancer development in the breast. Before this can be comprehended other facts equally essential remain to be learned. No matter whether it be used properly to elucidate the truth or employed to support unjustified hypotheses, it stands firmly as a fact and we owe these laborers a debt of gratitude for supplying it.

JOSEPH H. MORTON: I would like to ask Dr. Frantz one or two questions. I did not catch the average age of this group of 225 patients, though I assume it was pretty high. It has been noted that chronic cystic disease often undergoes involution following the menopause to the extent where previously well defined cysts on clinical examination are no longer palpable. Yet the evidence in some of the slides presented indicates activity that one would attribute to women much younger than sixty years. Could that not be due to the fact that the adrenal gland secretes a little estrogen even in the post-menstrual state? We know that over a period of many years this accumulated secretion may cause vaginal bleeding in a woman of seventy, and although the first impression would be malignancy, it occasionally turns out to be a hyperplastic endometrium. It seems clinically also, that there is a close relationship between chronic cystic mastitis and premenstrual tension and that the former may be an end result of recurrent episodes of the latter. In a current study of premenstrual tension in the reformatory and prison of Westfield State Farm it was found that 118 inmates of a total of 350 in the reformatory suffered from premenstrual tension. This group ranged in age from sixteen to thirty-one years with an average age of 21.4 years. In the prison 131 of 257 inmates suffered from this condition. Their ages ranged from eighteen to fifty-three years with an average age of 32.4 years. Thus premenstrual tension occurred in 33.7 per cent of the younger age group and in 51 per cent of the older group.

Some evidence has indicated that an estrogen-progesterone imbalance may be the cause of both these conditions,[3] and that the increased epithelial proliferation in the breast and uterus as well as the increased

retention of extracellular fluid are due to the unopposed action of a relative excess of estrogen.

VIRGINIA KNEELAND FRANTZ: I would like to comment on your questions, but I cannot really answer them, Dr. Morton. The clinicians certainly do feel that there is a disappearance of palpable irregularities in the breast after the menopause in a considerable number of cases. The difficulty, of course, is in knowing with what we are dealing. We cannot take out tissue for diagnosis and put it back for further observation. As we observe these patients in general I think we all feel that after the menopause their breasts do undergo involution in a very large number of cases, but not always. We had hoped to be able to document this by abstracting the case histories and correlating the histologic findings with the menstrual cycle and with possible administration of hormones given for the relief of menopausal symptoms. The study was exceedingly unrewarding. We could not make any correlation because of insufficient data. Foote and Stewart[2] in their analysis of 300 cancerous breasts came much closer to such correlation than we could because they were studying case histories which had been taken from the standpoint of breast disease. Their histories consequently had many more data about the hormonal status of the patients than ours had. I have come no closer to understanding variations in involution than to think they must be on some hormonal basis. Since it is the fashion nowadays to implicate the adrenal gland in pretty nearly everything, I suppose it might have something to do with it, but in my ignorance I cannot say anything more than that.

I have always wished to have time to undertake a study comparable to the painstaking work of Dr. Ingleby,[3] who has correlated the findings in breast tissue with the stage of the menstrual cycle. In her cases she obtained a very careful history pre-operatively and she took many sections of the breasts. Such an autopsy study might be rewarding but would be very laborious. In autopsy material we are not given historical facts concerning the menstrual cycle as we would like to have them. Also one would like to obtain repeated biopsies from an individual breast. It may well be misleading to compare a biopsy at one stage of the menstrual cycle with that of another patient in another stage.

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Clearing Technique in the Search For Lymph Node Metastases

ANALYSIS OF 75 RADICAL MASTECTOMY SPECIMENS

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The clearing technique was modified from the method used by Grinnell to clear specimens of carcinoma of the colon. Because of the abundant fat in the radical mastectomy specimen, the tissue that contains lymph nodes is dissected away from the breast and pectoral muscles. This tissue is then washed in water to remove as much blood as possible. It is oriented, pinned out on a cork board and fixed in formalin. After fixation the specimen is removed from the cork board. For rapid dehydration, the tissue is incubated at 62° C. in 80 per cent, 95 per cent, and absolute alcohol (2 changes) from 8 to 12 hours each. Between changes of alcohol, the liquified fat is squeezed out by hand. Following dehydration, the tissue is placed in cedar wood oil, and the lymph nodes are located by transmitting light through the specimen. The lymph nodes show up as dark, circumscribed nodules against a light background.

The seventy-five cases in which the specimen was cleared were compared with seventy-five cases in which the lymph nodes were dissected out in the fresh specimen. In the cleared group a total of 2653 nodes was found, an average of 35.3 nodes per case; whereas in the dissected group, there was an average of 21.5 nodes per case. More important, 27.7 per cent more involved nodes were found in the cleared group. This increase in total nodes found and total nodes involved is due largely to finding small nodes, some a fraction of a millimeter in diameter, which are not usually seen by the dissection method. Often these small nodes are from the upper part of the axillary dissection, and it therefore is important for prognostic purposes to know whether they contain cancer.

In the cleared group in 96 per cent of the cases there were more than 20 nodes each, while in the dissected group only 50 per cent of the specimens contained that many. Nevertheless, the percentage of cases with metastases to lymph nodes was not statistically increased. That is, 56 per cent of the cleared cases had lymph nodes that contained cancer, and in the dissected group 44 per cent had regional lymph node metastases. Of the total cases of radical mastectomy done in the Presbyterian Hospital up to 1935 approximately 60 per cent contained axillary lymph nodes involved by cancer.

An attempt was made to analyze the factors that contributed to the number of nodes found per case. Regardless of the age of the patient, the operator, or the breast involved, there was no appreciable difference in the number of nodes found. It should be stated that nearly all of the operators used the operative technique described by Haagensen. The presence of metastases in the nodes did not play a part except when an exceedingly large number of metastases was present. In the cleared group, the exceedingly large number meant that more than 30 nodes in a case contained metastatic cancer. In these cases a greater number of nodes was found per case.

There was an apparent correlation in the cleared group, between the size of the primary neoplasm and the number of nodes involved, i.e., the larger the tumor the more nodes involved. Also, when the cancer was undifferentiated there was a higher percentage of metastases than in the well-differentiated tumors. In colloid, solid circumscribed (medullary), and intraductile

carcinomas only 38 per cent of the cases had nodes involved by cancer. There appeared to be fewer cases with axillary metastases when the primary lesion was located in the lower quadrants as compared to the upper quadrants.

In conclusion, one can find more nodes and more involved nodes by clearing the axillary tissue of specimens from radical mastectomy for carcinoma of the breast. However, the percentage of cases with involved nodes is not significantly increased. The advantage of clearing the specimen appears to be the more accurate determination of the number and location of involved nodes. Prognosis can thereby be made with more assurance in each individual case.

DISCUSSION

ARTHUR PURDY STOUT: This has interested me a great deal, and I am glad Dr. Pickren has been doing it, because we have been anxious to know whether by the old technique we were finding all the metastatic nodes. The last time he presented it he said that he did not feel that he had found any cases so far where the method showed metastases where the ordinary dissection failed to find any. Is that true, or have you now found some in which you would not have found nodes by the older method?

JOHN W. PICKREN: There has not been a single case in which I have found metastases that would not have been found on dissecting the specimen. However, I have found more nodes that were involved than I would have found by the ordinary dissection method.

ARTHUR PURDY STOUT: The next step, which I believe will be much more arduous, will be to try and repeat Otto Saphir's method of serial section of the nodes to see whether that method will disclose more unsuspected metastases. I have forgotten what he reported, but it was an increase of something like 33 per cent, which seems almost incredible to us. Dr. Heineman, who is present tonight, and who is with me at the Delafield Hospital, has just started one or two cases. The trouble is that he has not yet arrived at a good rapport with the technician, who must be taught not to throw away any portion of the node in getting the microtome working well; if you are really going to do serial sections it is necessary to save all the scraps from the beginning to the end of the node. In large nodes that seems like a tremendous undertaking, especially in cases where the node is just a rim of lymphoid tissue surrounding a great mass of fat. If you should serially section that it would mean hundreds and hundreds of sections, and we so far have not made more than a half-hearted trial run of a case or two. Have you done more than one case?

DR. HEINEMAN: No.

ARTHUR PURDY STOUT: We learned from that one case how to avoid errors in the future, but somebody I think must repeat that investigation of Saphir's; otherwise it will stand as a condemnation of our present technique of examining lymph nodes for metastases.

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

AT THE ACADEMY – 4:30 P.M.

FRIDAY, DECEMBER 5, 1952

Subject: HEPATITIS AND CIRRHOSIS OF THE LIVER

Moderator: Franklin M. Hanger—Professor of Medicine, College of Physicians and Surgeons, Columbia University

Members: William J. Eisenmenger—Associate Physician to the Hospital of The Rockefeller Institute for Medical Research

Gerald Klatskin—Associate Professor of Medicine, Yale University School of Medicine

Arthur J. Patek, Jr.—Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University

Mary Ann Payne—Assistant Professor of Clinical Medicine, Cornell University Medical College

FRIDAY, JANUARY 9, 1953

Subject: HYPERTENSIVE VASCULAR DISEASE

Moderator: William Goldring—Associate Professor of Medicine, New York University Medical College; Visiting Physician, Bellevue Hospital

Members: Herbert Chasis—Associate Professor of Medicine, New York University College of Medicine

Arthur M. Fishberg—Director of Medicine, Beth Israel Hospital

George A. Perera—Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University

Edward Weiss—Professor of Clinical Medicine, Temple University School of Medicine

FRIDAY, FEBRUARY 6, 1953

Subject: DISORDERS OF THE BLOOD

Moderator: Claude E. Forkner—Associate Professor of Clinical Medicine, Cornell University Medical College; Physician, New York Hospital

FRIDAY, MARCH 6, 1953

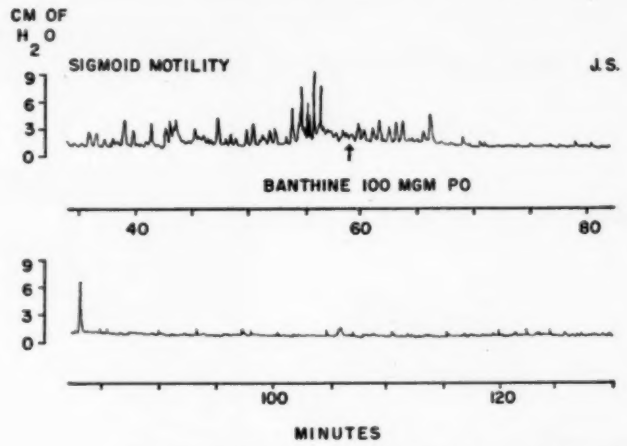
Subject: THE FAILING HEART

Moderator: Charles E. Kossmann—Associate Professor of Medicine, New York University College of Medicine

FRIDAY, APRIL 3, 1953

Subject: RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

Moderator: Charles Ragan—Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University



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2. Lepore, M. J.; Golden, R., and Flood, C. A.: Oral Banthine, an Effective Depressor of Gastrointestinal Motility, Gastroenterology *17*:551 (April) 1951.

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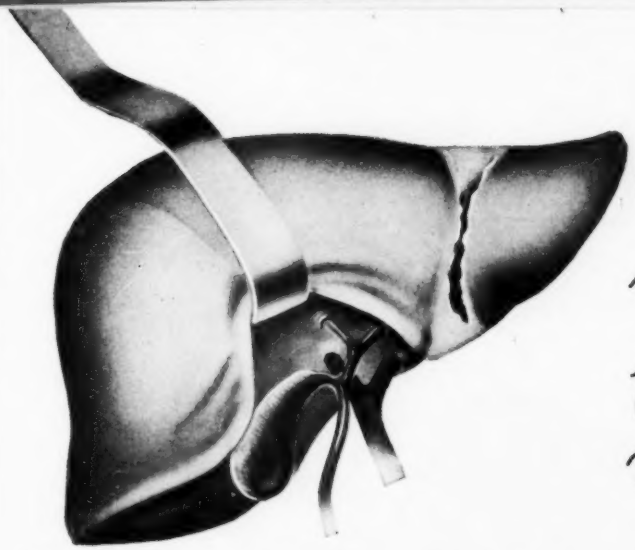

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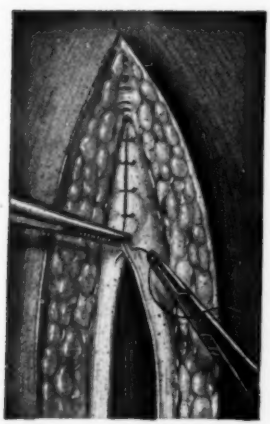

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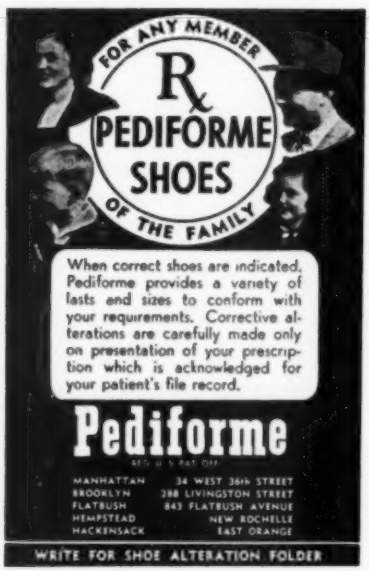
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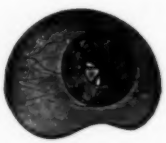

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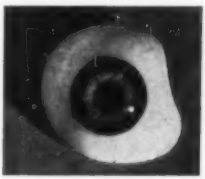

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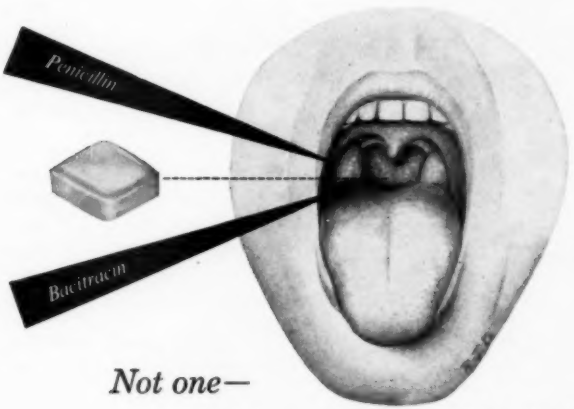

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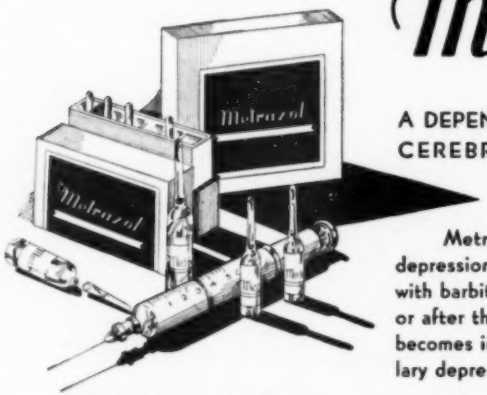
2. Bachman, M.C.: J. Clin. Invest. *28*:864 (Sept.) 1949.



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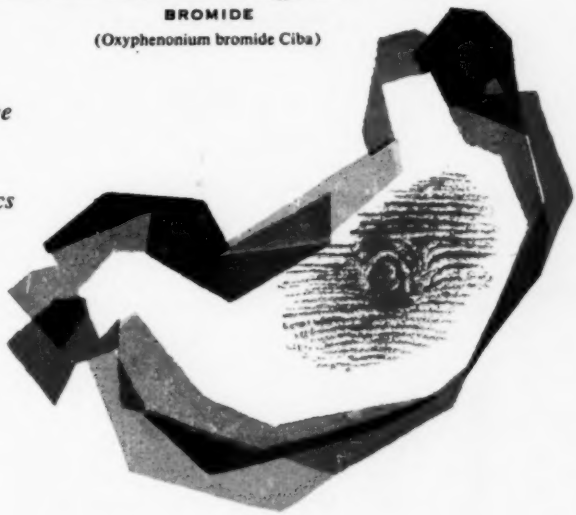

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1. Rogers, M. P., and Gray, C. L.; *Am. J. Digest. Dis.*, 19:180, 1952.

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1. *Seley, S. A.: Am. J. Dig. Dis. 13:238 (July) 1946.* 2. *Rossien, A. X.: Rev. of Gastroenterol. 16:54-58 (Jan.) 1949.* 3. *Rossien, A. X. and Victor, A. W.: Am. J. Dig. Dis. 14:226-229 (July) 1947.* 4. *Batterman, R. C. and Ehrenfeld, I.: Gastroenterol. 9:141 (August) 1947.*

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